Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Titanium dioxide

EC Number: 236-675-5
CAS Number: 13463-67-7

CLH-O-0000001412-86-163/F

Adopted
14 September 2017

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Titanium dioxide
EC number: 236-675-5
CAS number: 13463-67-7
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	United Kingdom		Individual	1
Comment received				
As he CLH report and decades of human health experience (CLH report p8 Carcinogenicity) Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. This type of scaremongering brings the work of the ECHA into disrepute and actually leads to detrimental effects on support for EHS awareness in the general public when products of extremely safe wide exposure (in almost every home there is a painted of plastic article containing titanium dioxide). Consequently, when the general public and workers see this sort of classification it is generally ignored with the risk that really dangerous substances are then also ignored.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	United Kingdom		Individual	2
Comment received				
As he CLH report and decades of human health experience (CLH report p8 Carcinogenicity) Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. This type of scaremongering brings the work of the ECHA into disrepute and actually leads to detrimental effects on support for EHS awareness in the general public when products of extremely safe wide exposure (in almost every home there is a painted of plastic article containing titanium dioxide).				

Consequently, when the general public and workers see this sort of classification it is generally ignored with the risk that really dangerous substances are then also ignored.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	Germany	Eternit GmbH	BehalfOfAnOrganisation	3
Comment received				
Eternit GmbH is following the German rules with exposure limits for Titanium dioxide: <1,25mg/m3 of respirable dust and <10mg/m3 of inhalable dust. Eternit GmbH uses up to 300tons Titanium dioxide per year. Eternit GmbH didn't observe any case of cancer caused by Titanium dioxide.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2016	Austria		BehalfOfAnOrganisation	4
Comment received				
TiO2 use is ubiquitous in our society. Most of the surfaces and items that are white in color contain TiO2. Thus,we are surrounded by TiO2 containing materials in our homes, workplaces and public areas. Since the introduction of TiO2 as a commercial product in 1923, there have been no identified health concerns associated with its exposure among consumers or the general population. Downstream users can also be exposed to TiO2 dust. Appropriate safe handling and use information are included in product documentation such as Safety Data Sheets (SDS). Consumer exposure to TiO2 dust is presumed to be very low because TiO2 is typically incorporated into a product matrix where it is tightly bound such as in paints or plastics. Thus, inhalation exposure is not considered as relevant for the general public! Based on existing safety information, it can be concluded that the use of titanium dioxide and it´s nanomaterial (ultrafine) as an ingredient in paints poses no risks to human health!				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	EuPC (European Plastics Converters	BehalfOfAnOrganisation	5

Comment received

The French agency ANSES is proposing a new harmonised classification for Titanium dioxide : "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B – H350i. This classification applied for both fine particles and nanomaterials of TiO2 without being able of any distinction in terms of morphology, crystal phase, and surface treatment. ".
This substance is used mainly as a white pigment, brightener or opacifier in most plastics applications. It also provides excellent UV stability important for outdoor applications.
In the plastics converting industry, most of the applications contain TiO2 substance. The plastics converting industry turnover is estimated at 280 billion € (Eurostat 2014). The impact upstream is not taken into account here but as an order of magnitude the whole plastics supply chain consolidated turnover is estimated at 350 billion € including polymer producers.

It is estimated that almost all the 50,000 companies in the plastics converting sector, mainly SMEs, may be potentially impacted in case the availability of titanium dioxide would become uncertain.

The classification dossier relies on a limited number of studies in animals either of low quality or with extreme doses provided which are not in relation with any foreseeable exposures.
In the plastics industry, exposure is effectively controlled today. There is today no alternatives with the same properties and those alternatives may not be better from environment or health point of view.
Classification and labelling of TIO2 would have disproportionate socio-economic effects compared to the expected health benefits and is not the most efficient measure to improve safety. In case of concern, the use of binding EU occupational exposure limits should be considered instead.

ECHA note – A confidential and a non confidential attachment were submitted with the comment above.
2013-07-15_TiO2 CLH comment EuPC_confidential.pdf
2013-07-15_TiO2 CLH comment EuPC_public.pdf

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	6

Comment received

General appraisal of the classification of Titanium dioxide (TiO2)
The classification of TiO2 will heavily impact the entire ceramic industry that is dealing with natural clays, bauxites and further raw materials belonging to the chemical System of SiO2-Al2O3, because TiO2 is a natural occurring impurity in all said materials. A classification of TiO2 in Carc. 1B would - according to the CLP-Regulation- require a classification of these natural materials and ceramic products as Carc. 1B and would also

render these raw materials and a lot of ceramic products to dangerous waste.
Beside natural occurring TiO2 predominantly mineralized as rutile the ceramic industry uses TiO2 as white pigment in glazes and engobes. There is no proper solution for a substitution available on the market that will be competitive with Products from outside EU. This will have a considerable strong impact on the industry branch that produces sanitary-ware, tableware and tiles, where already a strong competition exists with producers in Asia.
Conclusion
The classification of TiO2 as Carc. 1B is not the proper answer for better worker protection, as the same level of protection can be achieved by using more targeted directives on occupational safety and health (OSH) and effective and appropriate risk management measures for worker protection with less administrative costs, much less negative socio-economic consequences.

Dossier Submitter's Response

See points 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	European Expanded Clay Association	BehalfOfAnOrganisation	7

Comment received

TiO2 is present in the clay produced by expanded clay manufacturers. There are inconsistencies between the CLH report and ongoing scientific studies, in particular the 'one size fits all' approach adopted by the report. The proposed classification as cat 1B. carcinogenic is not supported by sound scientific evidence.

ECHA note – A non confidential attachment was submitted with the comment above.
16 07 15 Cerame-Unie comments to the proposed classification of TiO2.docx

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Cerame-Unie - The European Ceramic Industry Association	BehalfOfAnOrganisation	8

Comment received

Cerame-Unie, the European Ceramic Industry association, covers a wide range of products including bricks & roof tiles, clay pipes, wall & floor tiles, refractory products, sanitary ware, table & decorative ware, technical ceramics, expanded clay, abrasives and enamels. It accounts for more than 200 000 direct employments within the EU.

In addition to its wide spread use as a white pigment in the ceramics industry, a number of ceramic products (e.g. certain ceramic wall tiles or roof tiles) use TiO2 for surface coating based on its photocatalytic properties. TiO2 is present, in trace amounts, in a number of ceramic and clay processing plants. In enamel industry, titanium dioxide is

used approximately around 1000 tons per year. Titanium dioxide is also an essential raw material for the production of different types of abrasive products (inorganic bonded abrasives, organic bonded abrasives and coated abrasives) for the European abrasive industry.

Titanium dioxide is also present, up to 4%, in a number of naturally occurring minerals that are used in the refractory industry such as refractory calcined clay (chamotte), calcined bauxite, brown fused alumina, andalusite, zircon silicate, synthetic mullite, refractory clay ,… As a result, the proposed classification would impact 40 to 50% of all refractory products.
The CLH dossier proposes the same classification for all forms of TiO2. This goes against the scientific conclusions drawn by Wang and Fan in 2014 (International Journal of Molecular Science, 2014, 15, 22258-22278; doi:10.3390/ijms151222258; article entitled: Lung Injury Induced by TiO2 Nanoparticles Depends on Their Structural Features: Size, Shape, Crystal Phases, and Surface Coating).

No cases of pulmonary fibrosis were observed among TiO2-exposed employees. The study of Dupont "Epidemiologic study of workers exposed to titanium dioxide." J Occup Med. 1988 Dec;30(12):937-42 gave the same result. We believe that a harmonised classification of TiO2 as a carcinogen cat. 1B can only be supported if there is unequivocal data supporting the classification, which we consider is not the case in the CLH dossier on TiO2 as presented by France.

We also understand that ECHA is finalizing a dossier evaluation for TiO2 and France itself has notified its intention to conduct a substance evaluation on TiO2 in 2017. Therefore, we believe that no regulation should be proposed until these studies are complete, and that both traceable mineral standards and a methodology for the analysis of the material should be developed at EU level.
Cerame-Unie fully supports the general and specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA), the Titanium Dioxide Industry Consortium (TDIC) and the Industrial Minerals Association (IMA-Europe).

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	AFCA (Spanish Association for Food Additives and Food Suplements Manufacturers &Traders	BehalfOfAnOrganisation	9

Comment received

July 15, 2016
Re: Comments from AFCA(Spanish association for food additives and food supplements manufacturers & traders) to send ECHA on "Proposal for a Harmonized Classification and Labelling of TiO2 as a category 1B carcinogen"
To whom it may concern:
AFCA as (Spanish association for food additives and food supplements manufacturers & traders), that concerns the use and colours food application and

particularly the mineral colour E171(TiO2), that has been otorgued an ADI by EFSA of NS(Not specified) due its high safety level demonstrated through a full assessment on the application on foodstuffs, made by EFSA.
Accordingly the above scientifc mention, the impact of TiO2 on foods must be considered negligible.
The mention on exposure toxicity potentially produced by inhalation is unrelevant on food industry at normal consumers consumption intended foods intake, due the normal use conditions.
The classification of TiO2 as a Cat. 1B carcinogen is duplicative of existing classification by the International Agency on Research on Cancer (IARC) as Group 2B carcinogen via inhalation.
The International Association of Color Manufacturers (IACM) is the trade association that represents the manufacturers and end-users of coloring substances that are used in foods globally, including natural and synthetic colors such as titanium dioxide (TiO2). Our aiming is to send the necessary comments in response to ANSES Proposal to ECHA for a Harmonized Classification and Labelling of TiO2 as a category 1B carcinogen with Hazard Statement H350i: "May cause cancer by inhalation".
It becomes clear, through the scientific available documents, that no evidences existing against the food use for TiO2.
Of course AFCA would also like to offer support of the comments submitted by the Titanium Dioxide Manufacturers Association (TDMA) and those submitted by IACM member company Colorcon.

Sincerely,
<confidential>

Dossier Submitter's Response

See point 1 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

Please note that although there is a strong link between CLP and IARC classification criteria regarding the definition of "evidence", interpretation of "sufficient" and "limited" can differ. Furthermore, additional criteria are taken into account in CLP decision. Finally, IARC classification has no regulatory impact.

RAC's response

Noted. The opinion compares the IARC assessment with the RAC proposal. With specific reference to comment 9: It is clearly expressed in the opinion that the carcinogenicity profile observed is specifically related to inhalation (to respirable TiO2 particles).

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	Hanno-Werk GmbH & Co.KG	BehalfOfAnOrganisation	10

Comment received

TiO2 has been used by our company for many years without any problems.
A classification of TiO2 with Carc. 1B and H350i means that every product containing more than 0,1% TiO2 has to be labeled with "Danger", "GHS08" and H350i. This means almost every product containing TiO2 has to be labeled like that no matter if ist dusty or not.
And this means that almost every product containing this minimum amount of TiO2 will get restrictions in selling to customers.
As ist allready written, there is no evidence, that any product containing TiO2 has caused cancer. Not a single case is known.
And the costumers using products containing TiO2 will not come in a situation like mice in

a TiO2 dust filled air. TiO2 is bound in liquids and pastes, there is simply no TiO2 dust. Because of this and the fact that there is no sufficient replacement for TiO2 at the time we support any position which does not has to lable products containing TiO2 in liquid or pasty form
Dossier Submitter's Response
See point 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	GSB International	BehalfOfAnOrganisation	11
Comment received				
I represent GSB International, 1977 established in the EU Member State Germany and respond on behalf of that quality association. Our members are manufacturer and user of coating material containing titanium dioxide pigments and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. TiO2 is a key material to manufacture powder and liquid coatings. This coating material is applied to metal constructions in a coating plant. We understand that the consequence of the proposed classification would negative is affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our member companies as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	IBIDEN Porzellanfabrik Frauenthal	BehalfOfAnOrganisation	12
Comment received				
Our company is a leading manufacturer for environmental catalysts based on Anatase. This type of catalysts is the only one who is economically able to reduce Nitrogen Oxide emissions from industrial exhaust gases e.g. from power generation plants. Over 30 years, we processed more than 50.000 t of Anatase raw material. Medical controls of workers did not indicate any lung disease caused by dust from our production processes				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	Wirtschaftskammer Österreich (WKÖ)	BehalfOfAnOrganisation	13
Comment received				
Please, see document attached. The pull-down menu does not include a suitable option for WKÖ, which is a public body. I have picked national authority since this is the closest to our status. We definitely are not an industry/trade association, NGO, company nor a academic institution. It would be useful, if you could extend this menu at least to an option called "other" or even better "public body". ECHA note – A non confidential attachment was submitted with the comment above. su_133_StN_WKÖ Titanoxid.pdf				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		BehalfOfAnOrganisation	14
Comment received				
As a formulator of paints we are strongly concerned regarding the proposed classification of titanium dioxide as Category 1B carcinogen. We are not aware of any relation between the use of TiO2 and the development of cancer by our workers in our long years of using TiO2. Also, after consulting with our suppliers they confirmed to us that they checked the available scientific data and still consider TiO2 non-hazardous. Because the proposed classification would result in a classification of most of our products as well, we are expecting a huge fallout. (E.g. the ban of most of our decorative and automotive refinishing paints and a limited marketability of our industrial paints)				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States		Individual	15
Comment received				
Assessing the Pulmonary Carcinogenicity of Inhaled TiO2 Particles by <confidential> A. Comments on CLH Proposal "Harmonized Classification and Labelling" General: As Inhalation Toxicologist, my main concerns when designing, reviewing or interpreting				

inhalation studies are relevant and appropriate considerations of dose-related issues. These include dosimetry, dosemetric and dose-rate as fundamental principles in toxicology.
I offer the following critical remarks on the CLH proposal: Effects of TiO2 in the respiratory tract observed in the selected publications are summarized in the CLH proposal without consideration of the doses used, no critical comments on the appropriateness/relevance of concentrations/doses vis-à-vis realistic concentrations are provided. The concept of lung particle overload is not described well, no mention is made of Morrow's pioneering publication (1988) where he described this phenomenon observed in rats exposed chronically to high concentrations of poorly soluble particles of low cytotoxicity (PSP). Although important concepts related to the overload hypothesis are addressed, conclusions drawn with respect to inter-species extrapolation of effects observed in rats are not scientifically justified.
The proposed classification as a Category 1B carcinogen for TiO2 according to EU regulations is apparently mandated by the finding of induction of lung tumors in one species following one chronic inhalation and one instillation study performed at extraordinary high concentrations/instillations. It is somewhat confusing when on the one hand the opinion generally shared by the scientific community ¬– that PSP overload-induced effects in rats are due to indirect secondary inflammation based genotoxic events – is accepted, yet on the other hand extrapolation of the tumorigenic effects to humans is advocated. Both OECD and ECHA guidelines advise against using results of excessive, high concentration rat inhalation studies as relevant for defining a carcinogenic human hazard. As shown by the Lee et al. (1986) two-year rat inhalation study, rats at the high overload-inducing concentrations of 10 and 50 mg/m3 did not induce lung tumors, and only the extraordinary, excessive concentration of 250 mg/m3 induced lung tumors. Thus, as discussed in more detail before (Oberdörster, 1995), inhalation of chronic high concentrations of PSP by rats inducing overload does not generally induce lung tumors in this species; this is similar to other mammalian species, mice and humans, for which there is no evidence of PSP-induced carcinogenicity despite particle overload-induced impaired particle lung clearance. It is only the rat which responds with lung tumors when retained PSP lung burdens exceed by far (orders of magnitude) an MTD. When designing long-term rat inhalation studies with PSP it is, therefore, mandatory to carefully consider that the highest exposure concentration does not exceed the MTD or MFTD (maximum functionally tolerated dose) as defined by Muhle et al. (1990).
As indicated before, it appears that the authors of the CLH proposal on the one hand made some effort to generally accept the prevailing view in the scientific community that the underlying mechanism of TiO2-induced lung tumors in rats is due to secondary genotoxicity via the induced inflammation and the associated oxidative stress generation by inflammatory cells (PMN in particular). On the other hand, the view is expressed in the final conclusion of the proposal, that high particle overload induced lung tumors in the rat are indeed to be used for identifying a potential carcinogenic risk for humans, without providing further justification. Scientifically, this is not justifiable, and I strongly agree with the generally accepted view of the scientific community that the existing EU carcinogenic classification scheme does not apply to TiO2 and other poorly soluble particles of low cytotoxicity. Rather, a classification based on non-neoplastic effects – e. g. inflammation, granuloma formation, fibrosis – according to GHS and CLP regulation should be utilized.
Besides being scientifically not supportable, a carcinogen classification of TiO2 completely ignores the fact that no epidemiological evidence of PSP-induced lung cancer in TiO2-exposed workers or even in clearly particle-overloaded lungs (take the example of coal miners) exists; indeed, epidemiological studies in coal miners show that apparent heavy inflammatory lung conditions (coal workers pneumoconiosis) is not correlated with lung cancer. Apparent inconsistencies – like on the one hand admitting a secondary genotoxic mechanism and then insisting that primary genotoxic mechanism cannot be ruled out -

are also evident in other sections, for example, when the importance of particle surface area as dosemetric is pointed out, but then this important concept is not applied in the end with respect to categorizing retained doses. ECHA note – A non confidential attachment was submitted with the comment above. CLH Report Comments_(confidential) 7 15 16.pdf
Dossier Submitter's Response
See points 1, 3, 2 and 4 of the attachment to the RCOM. Regarding proposed classification based on non-neoplastic effects: Due to ongoing discussions on adequate metrics for nanomaterials, it is not clear if comparison to cut-off values for STOT RE classification is relevant to TiO_2 as nanoparticles. Since the proposed classification as carcinogen is judged appropriate for TiO_2, the resulting risk mitigation measures would cover those induced by a STOT RE classification. Thus, it was not deemed necessary to assess if criteria for STOT RE are fulfilled.
RAC's response
RAC was mandated to give an opinion on carcinogenicity. RAC did not discuss a STOT RE classification.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Canada	Rio Tinto Iron & Titanium	BehalfOfAnOrganisation	16

Comment received
Rio Tinto Iron & Titanium is a world leader in feedstocks production for the titanium dioxide industry since 1950. Our wide range of products is processed by our customers for the production of titanium dioxide pigment (TiO2). Under REACH regulation, Rio Tinto Iron & Titanium is the SIEF lead registrant for the substance UGI (slags, ilmenite electrothermal smelting, EINECS: 293-671-6). The proposed ANSES classification for TiO2 will affect the REACH dossier for UGI directly, since a complete read-across approach with TiO2 was applied for all routes of exposure. It will also affect other titanium feedstocks (ilmenite, rutile…) that were not registered under REACH since they were considered as ores and concentrates. The proposed classification will therefore have a direct impact on the overall titanium feedstocks industry, specifically for the feedstocks entering the EU market. Rio Tinto Iron & Titanium understand and agree with the rationale behind the TDMA/TDIC position of no classification for TiO2 and fully support it. <confidential>
Dossier Submitter's Response
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99. Please note that the classification proposal only concerns the inhalation route.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom		BehalfOfAnOrganisation	17
Comment received				
This business employs 187 people in Europe. We manufacture wallcoverings. Titanium Dioxide is an important component of our products and it is great concern to us if this material were to be classed as a carcinogen. We have used TiO2 within our products for over fifty years and during this time we have followed all statutory requirements for dust control and we are unaware of any health issues experienced by our employees through exposure to TiO2 in the workplace. The prospect that we may have to label our rolls of wallpaper as containing a carcinogen will potentially cause customers to stop buying our products due to misplaced concerns about a hazard when the potential for exposure to that hazard is very low. Substitution of TiO2 for other materials would not be economic and will raise the cost of products at a time when the whole of Europe does not need any further inflationary pressures. This proposed re-classification if adopted will decimate the DIY industry in Europe				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Italy		BehalfOfAnOrganisation	18
Comment received				
I represent the company <confidential> established in the EU Member State ITALY and I respond on behalf of that company. We are a formulator of paints, varnishes and liquid applied waterproofing membranes and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 40 people. We have been using this substance for 30 years. As we successfully manage the workplace exposures of dust (by the usage of cyclone separator), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (we don't understand the relation existing between the hazard in handling TiO2 in powder form and in handling liquid TiO2-containing produtcs) and to our company (our business depends in large amount on TiO2 and we are not aware of an effective alternative).				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		BehalfOfAnOrganisation	19
Comment received				
We support the comments provided by the TDMA/TDIC trade associations. In addition, as downstream user, we are concerned about the impact of the proposed classification on mixtures and indirectly on products through black listing. When TiO2 is				

embedded in a polymer matrix there is no potential for inhalatory exposure anymore. The particles possibly formed through abrasion or degradation would not have the same properties as pure TiO2. There is in that case no justification to classify and label mixtures as carcinogen (by inhalation). This should be taken into account when the proposed classification is discussed.
Dossier Submitter's Response
See point 1 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Henkel AG & Co. KGaA	BehalfOfAnOrganisation	20
Comment received				
Henkel is a leading EU manufacturer of cosmetics, household detergents & cleansers, and adhesives & sealants (including consumer, professional and industrial products). We are using titanium dioxide in a wide variety of products of all three business units. The main use by volume is as white pigment. For detailed information on the use of titanium dioxide in those industries, please see the comments provided by the industry associations Cosmetics Europe, AISE and VCI. We participated in developing those positions and fully support their conclusions. We are also part of the Titanium Dioxide Industry Consortium (TDIC) for registration of titanium dioxide under REACH. For the majority of our applications, titanium dioxide cannot be replaced due to superior performance as a pigment. Therefore, our in-house toxicologists were closely monitoring the scientific discussion on the carcinogenic properties of titanium dioxide, especially in the context of safety of nanotechnology. The CLH report submitted by ANSES is based on several toxicological and regulatory assumptions and interpretations that are in contradiction to well established scientific positions and practice in classification of chemicals (see below). Those points of discussion are of general methodological nature and go far beyond the classification of titanium dioxide. Therefore, we strongly think that classification of titanium dioxide based on those assumptions and interpretations is not justified, unless general clarification will be reached on these topics. The contradictions we are referring to are the following: The proposed classification is mainly based on two well-known inhalation studies reporting lung tumors in an overload context (see CLH report p. 8). Those health effects of poorly soluble particles in the context of lung overload were intensively discussed earlier and concluded as not relevant for human beings (see e.g. ECETOC Technical Report 122). For a detailed discussion of the state of science, please see the comment provided by TDMA/TDIC and references therein, which we fully support. The submitted CLH report does neither include new scientific data nor add relevant new scientific aspects to the interpretation of those data. Thus, the contradicting interpretation and the concluded classification proposal seem to be inadequate from a toxicological point of view. Furthermore, the CLH report explicitly acknowledges that the reported health effect is not specific to titanium dioxide, but rather typical to inflammatory processes and oxidative stress induced by poorly soluble particles. However, from a regulatory standpoint, the aim of CLP is to classify intrinsic properties of chemicals rather than hazards related to the physical state of a material. Therefore, e.g. dust explosion – obviously a severe safety				

risk when operating chemicals – is included e.g. in the US HMIS system (focusing on occupational risk) but not in GHS and CLP (focusing on intrinsic hazards of chemical substances), as the risk of dust explosion is due to the physical state of matter rather than to the intrinsic properties of the chemical. Accordingly, a potential cancer risk of poorly soluble particles (if existing) should be addressed by means of occupational safety regulations rather than by harmonized classification under CLP (for comparison see regulation of hardwood dusts under 2004/37/EC). The major potential risk of exposure to titanium dioxide dust (if at all) is handling of dry titanium dioxide in production. Harmonized classification of titanium dioxide as Carc. 1B, however, will automatically trigger a set of restrictions mainly focusing on the end-user and especially the consumer, i.e. restriction for the use in consumer products under REACH Annex XVII and under the Cosmetics regulation. Whereas the proposed classification clearly refers to exposure by inhalation only (Carc. 1B - H350i: May induce cancer by inhalation), those restrictions, however, do not know a differentiation by exposure route. Thus, also uses without any inhalation risk would nevertheless be fully included into these restrictions. As a matter of fact, the by far main use of titanium dioxide as white pigment typically requires the pigment to be imbedded in some kind of matrix (e.g. paints, coatings, sealants, creams, fluids). Inhalation of titanium dioxide particles from such matrices is limited to a minimum (if not impossible) and will definitely never reach lung overload concentrations. For more specific uses in cosmetics (e.g. UV filter), respective safety assessments by the SCCS do exist and cover the inhalation risk (for details see the comment provided by Cosmetics Europe). Thus, the automatic restrictions resulting from harmonized classification as Carc. 1B are inadequate with respect to the identified exposure route and do not increase consumer safety (if a cancer risk by inhalation actually exists). However, due to the wide spread use of titanium dioxide as white pigment, and missing alternatives for substitution due to performance as well as safety reasons, the proposed classification as Carc. 1B and the resulting (ineffective) restrictions would have severe impact on many industries (for details on the use of titanium dioxide in various industries, please refer to the annex of the comment provided by VCI).

As a conclusion, we consider the proposed classification as Carc. 1B – 350i for titanium dioxide as scientifically not justified (as lung overload effects in rats are not relevant to humans), as inadequate in the meaning of CLP (as the reported effect is not an intrinsic property of titanium dioxide but an unspecific effect of the physical state of matter), and inefficient with respect to risk mitigation (as the resulting restrictions will mostly affect uses that are irrelevant with respect to a potential risk by inhalation).
Since the proposed classification is contradicting to established general understanding of classification practice - and the resulting restrictions would have severe impact on many industries -, we suggest to (if needed) discuss and clarify first the underlying general questions, i.e. relevance of lung overload effects to humans, relevance of unspecific effect of the physical state of matter for CLP classification, and impact of unspecific restrictions resulting from classification for highly specific exposure risks, before building classification of defined substances on it.

A potential cancer risk by inhalation of titanium dioxide particles (if existing) should be addressed by respective occupational exposure limits, as this addresses the (potential) risk where it is relevant.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	DAW SE	BehalfOfAnOrganisation	21
Comment received				
I respond on behalf of DAW SE. That company with its head quarter and some production sites is established in Germany, a full EU Member State. Besides Germany we have production sites in EU Member States Austria, France, Sweden, Italy, Romania and Poland. Company is a Downstream User formulating indoor and outdoor wall paints, plasters, renders, grouts, putties, fillers, varnishes, glazes, lacquers and other materials for European construction industry. We are highly concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs about 6,000 people in nearly all EU Member States. TiO2 is a key material to manufacture our high quality products. Neither in the Moment nor in midterm future, i.e., Minimum the next 10 years we do not see a white pigment which would be able to replace TiO2. Thus, we are concerned about the consequence of that proposed classification that would negatively affect our production and our markets. Regarding the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy and the whole construction industry in Europe. E.g., in German construction industry about 2.7 Million people work in nearly 580,000 entrepreneurships, i.e. mostly in SME.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	Cristal Pigment UK Limited	BehalfOfAnOrganisation	22
Comment received				
In over 60 years of manufacturing titanium dioxide at our facility in Stallingborough UK, there has been no particular health problem linked to working with titanium dioxide. Cristal is in complete agreement with the response to this consultation provided by the TDMA/TDIC submitted on 14th July 2016. Our opinion is that the CLH report reflects an inaccurate and misleading picture of the alleged inhalation carcinogen hazard presented by titanium dioxide for the reasons given in the TDMA/TDIC General Comments which were concluded as: • Due to significant and recognized deficiencies, the intratracheal instillation studies referenced by the CLH report do not qualify as supporting evidence and should therefore be discounted. • Interspecies differences in lung responses of rats versus other rodents, triggering different adverse outcome pathways (AOPs) demonstrating that the rat is uniquely sensitive. • The CLH report fails to recognize and assess the importance of the unique pulmonary reactions in long-term inhalation studies in rats that are fundamentally different in particle reaction and deposition compared to nonhuman primates and coal workers. • The CLH report fails to recognize the critical importance of enhanced translocation of particles to the lung interstitium, which correlates with the morphometric data in nonhuman primates and coal workers and differs from that of the rat. This difference is clearly demonstrated by the internationally recognized and accepted ICRP Human				

Respiratory Tract model.
• The CLH report fails to recognize the pathological analyses of lung tumours in rats exposed to PSPs of low cytotoxicity versus humans exposed to cigarette smoke and asbestos, which demonstrate different lesion types and locations in the respiratory tract.
• The CLH report also fails to adequately assess the importance of the numerous epidemiological studies of more than 24,000 workers that demonstrate no correlation between long-term exposures to titanium dioxide and lung tumours or other chronic lung disorders.
• The CLH report does not adequately assess the available genotoxicity database that demonstrates a lack of a primary genotoxic potential for titanium dioxide.
• The CLH report does not comply with ECHA Guidance on the preparation of dossiers for harmonised classification and labelling. It relies on studies using excessive doses; it fails to consider recent (negative) human epidemiological evidence, although reported in the REACH Registration dossier; and it fails to adequately assess the genetic toxicity database by explicitly limiting its assessment of in vitro data to the period 2010-2015, thus ignoring in vivo and in vitro data published prior to this period as well as data included in the titanium dioxide REACH registration dossier.

Dossier Submitter's Response

See response to TDMA/TDIC comment No. 99.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	23

Comment received

Für das Maler- und Lackiererhandwerk ist das Weißpigment Titandioxid - seitdem es industriell hergestellt wird - von elementarer Bedeutung. Beschichtungen mit dekorativen und schützenden Funktionen sind weit überwiegend mit Titandioxid pigmentiert. Das betrifft nicht nur die weißen Beschichtungen auf Außen- und Innenflächen (Bauwerke, Fahrzeuge, Anlagen), sondern zusätzlich auch viele mit farbigen Pigmenten rezeptierte Produkte.

Es gibt kein anderes Weißpigment mit nur annähernd vergleichbarem Deckvermögen und Weißgrad, das auch aufgrund seiner Stabilität (TiO2 ist chemisch inert) so universell in Beschichtungsstoffen eingesetzt werden kann.

Nachweislich durch Titandioxid verursachte Erkrankungen sind im Maler- und Lackiererhandwerk in Deutschland nicht bekannt. Eine Berufserkrankung durch Titandioxid ist nicht beschrieben. Diese Stellungnahme stützt sich dabei auf Erfahrungen des nationalen Spitzenverbands als Vertreter von ca. 40 000 Unternehmen im Maler- und Lackiererhandwerk mit ca. 200 000 Beschäftigten, die regelmäßig - in vielen Fällen beinahe täglich - mit TiO2-haltigen Produkten umgehen. Dies inzwischen seit einigen Generationen. Bestätigt wird dies auch von der für das Maler- und Lackiererhandwerk zuständigen gesetzlichen Unfallversicherer, der BG Bau.

Das Weißpigment ist zwar in den verarbeitungsfertigen Produkten regelmäßig gebunden, eine gelegentliche Exposition ist allerdings nicht vollständig zu vermeiden, wenn TiO2-haltige Beschichtungen abrasiv bearbeitet (z. B. geschliffen) werden müssen. Den Schutz der Beschäftigten durch inhalative Exposition haben die Arbeitgeber durch Einhaltung des

allgemeinen Arbeitsgrenzwertes für alveolengängige Stäube (A-Staub, in D derzeit 1,25 mg/m³) ohnehin sicherzustellen.

Durch eine Einstufung von TiO2 als Stoff mit kanzerogener Eigenschaft sehen wir außerdem auch zahlreiche Anwendungen aufgrund der photokatalytischen Eigenschaften des Oxids gefährdet, zumindest aber beeinträchtigt. Aufgrund der Nutzung der Katalysatoreigenschaft zum Abbau von Schadstoffen in der Atmosphäre (auch im Wasser) durch Beschichtungen konnten in den letzten 20 Jahren viele neue erfolgreiche Produkte mit zusätzlicher technischer Funktionalität etabliert werden, die zu einem Teil auch vom Maler- und Lackiererhandwerk appliziert werden.

Die schädigenden Folgen der vorgeschlagenen Einstufung aufgrund von zusätzlichen Beschäftigungsbeschränkungen, Aufbewahrungsverpflichtungen etc. wären für die Branche aber auch für den Verbraucher ganz erheblich.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom		BehalfOfAnOrganisation	24

Comment received
'I represent the company (Confidential) established in the EU Member State United Kingdom and respond on behalf of that company. We are a formulator of Coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs ~55 people. We have been using this substance for >18 years. As we successfully manage the workplace exposures of dust (refer to aspect 2 detailed in page 1), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public, refer to aspect 3, detailed in page 1) and to our company' (refer to aspect 4, detailed in page 1).
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France	EPSOM	BehalfOfAnOrganisation	25

Comment received
We consider the submitted proposal for a classification of titanium dioxide as carcinogenic category 1 B neither justified nor appropriated from the toxicological perspective (no indications of problems from epidemiological studies and application practice, results from "lung overload" studies in rats should not be transferred to humans…). We refer to the detailed toxicological assessment of TDMA (Titanium Dioxide Manufacturer Association). Such an inappropriate classification would have very serious negative socio economic

impacts on the European and French market as industrial and professional applications as well as consumer uses are numerous.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France	Cristal France SAS	BehalfOfAnOrganisation	26

Comment received

In over 90 years of manufacturing titanium dioxide at our facility in Thann, France, there have been no particular health problems linked to working with titanium dioxide.

Cristal is in complete agreement with the response to this consultation provided by the TDMA/TDIC submitted on 14th July 2016. Our opinion is that the CLH report reflects an inaccurate and misleading picture of the alleged inhalation carcinogen hazard presented by titanium dioxide for the reasons given in the TDMA/TDIC General Comments which were concluded as :

- Due to significant and recognized deficiencies, the intratracheal instillation studies referenced by the CLH report do not qualify as supporting evidence and should therefore be discounted.
- Interspecies differences in lung responses of rats versus other rodents, triggering different adverse outcome pathways (AOPs) demonstrating that the rat is uniquely sensitive.
- The CLH report fails to recognize and assess the importance of the unique pulmonary reactions in long-term inhalation studies in rats that are fundamentally different in particle reaction and deposition compared to nonhuman primates and coal workers.
- The CLH report fails to recognize the critical importance of enhanced translocation of particles to the lung interstitium, which correlates with the morphometric data in nonhuman primates and coal workers and differs from that of the rat. This difference is clearly demonstrated by the internationally recognized and accepted ICRP Human Respiratory Tract model.
- The CLH report fails to recognize the pathological analyses of lung tumours in rats exposed to PSPs of low cytotoxicity versus humans exposed to cigarette smoke and asbestos, which demonstrate different lesion types and locations in the respiratory tract.
- The CLH report also fails to adequately assess the importance of the numerous epidemiological studies of more than 24,000 workers that demonstrate no correlation between long-term exposures to titanium dioxide and lung tumours or other chronic lung disorders.
- The CLH report does not adequately assess the available genotoxicity database that demonstrates a lack of a primary genotoxic potential for titanium dioxide.
- The CLH report does not comply with ECHA Guidance on the preparation of dossiers for harmonised classification and labelling. It relies on studies using excessive doses; it fails to consider recent (negative) human epidemiological evidence, although reported in the REACH Registration dossier; and it fails to adequately assess the genetic toxicity database by explicitly limiting its assessment of in vitro data to the period 2010-2015, thus ignoring in vivo and in vitro data published prior to this period as well as data included in the titanium dioxide REACH registration dossier.

Dossier Submitter's Response
See response to TDMA/TDIC comment No. 99.

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	International Paint and Printing Ink Council (IPPIC)	BehalfOfAnOrganisation	27
Comment received				
ECHA note - Only a non confidential attachment was submitted. FINAL IPPIC Comments on ECHA TiO2 Consultation 7-15-16.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	European Coil-Coating Association	BehalfOfAnOrganisation	28
Comment received				
The European production of coil-coating industry represents a painted surface of more than 1.5Mm²/year and the order of magnitude of the incomes of the coil-coated metals in Europe is above 10,000 M€/year. The activity is (part of) the core business of more than 60 companies and more than 4000 people are directly working on coil-coating lines (and of course far more workers are surrounding the production line itself). The coil-coating sector in Europe is fully depending on the availability of TiO2. TiO2 is used in approximately 100% of the order-book of the pre-painted metal manufacturers since this pigment is used not only for the whites but also as a base pigment (along with black) to which other pigments are added to gain the final colour and obtain the correct colour saturation. There is no suitable known alternative at the moment, other pigments either give rather poor technical results or are classified as more hazardous. For these reasons, the coil-coating sector is obviously very attentive to the current comments about the proposal of a change of classification of TiO2. We carefully read the position paper from the TDMA and the coil-coating sector supports this position paper.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Switzerland		BehalfOfAnOrganisation	29
Comment received				
Any proposed harmonised classification for TiO2 for endpoints linked to its particulate properties must include a threshold concentration to separate the classification from bulk forms (e.g. the classification does not apply to TiO2 with <X% respirable particles), similar in fashion to CLP Annex VI entries with Note P or Note L. Precedent has been set				

for particle size dependent harmonised classification with metal powders (e.g. CLP Annex VI, Index No. 012-001-00-3, or 028-002-01-4).
Dossier Submitter's Response
See point 1 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	American Coatings Association	BehalfOfAnOrganisation	30
Comment received				
These comments are being provided by the American Coatings Association, Inc. (ACA) in response to the European Chemicals Agency (ECHA) open public consultation on the proposal from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) to classify all forms of titanium dioxide as a Category 1B carcinogen, by inhalation. The impact of this could mean that products formulated with Ti02 would not be permitted for sale to the general public in a major market (EU), as well as require additional and unnecessary special controls for professional/industrial users. Titanium dioxide is an essential raw material for the paint, coatings and ink industries, and is used in over 85% of our products. It provides key properties to our products, such as whiteness, opacity, brightness, protection from UV light, stability and durability. It is the most efficient and optimal way to provide an opaque white or colored layer for decoration and protection for walls, metal objects, plastic films, and other substrates The evidence provided by the French authorities is disputed by the coatings, plastics, cosmetics and food and drink industries in Europe, as well as the Ti02 manufacturers. We especially note the comments issued by the Titanium Dioxide Manufacturers Association (TDMA), various individual producers of TiO2, and our own affiliated global trade association, the International Paint and Printing Ink Council, Inc. (IPPIC). We endorse these comments and urge ECHA to consider them in the development of a final decision rejecting the proposed classification.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	International Paint and Printing Ink Council (IPPIC)	BehalfOfAnOrganisation	31
Comment received				
The paint and printing ink industries extensively utilize TiO2 in a wide variety of forms to make nearly all its finished products (preparations). TiO2 is considered the primary pigment for paints and coatings, providing for essential functionalities of hiding and coverage. Paints and coatings cannot be manufactured without this material. TiO2, along with a wide variety of other raw materials feedstocks are critical to our industry, where good manufacturing practices ensure safe use, including protections of worker health and product safety. In general, IPPIC stresses that inherent and undeniably relevant findings from human				

epidemiology studies, findings which embrace both hazard and (exposure) risk, must be considered as most authoritative in any effort to establish a meaningful classification. Animal studies, with their own acknowledged interpretive ("risk") issues (i.e. questionable findings arising from exceedance of the Maximum Tolerated Dose (Exposure), MTD) have more limited utility, and least informative of all are general inferences arising from mechanistic studies (which often are merely speculative, in particular in the absence of any corroborating (or relevant) animal or human data). To be clear, published epidemiology studies on the health of our industry's workers have not identified cancer risks associated with well documented and quantified exposures in the workplace, and these studies have been reinforced in three separate, independent evaluations of the literature by IARC (http://monographs.iarc.fr/ENG/Publications/List-of-Volumes.pdf). IPPIC notes that every epidemiology study of paint manufacturing workers has evaluated the impact of all exposures (risk) arising in the workplace, including exposure to TiO2 particulates. Accordingly, we strongly believe this human data offers a clear indication that the proposed classification is not appropriate. While these epidemiology studies on paint manufacturing workers are especially informative, they evaluate both the potential human health hazard (cancer endpoints) but also embrace the associated exposures (risk). These studies have enabled an overall conclusion by IARC that (work in) paint manufacturing is "unclassified" with respect to human cancer. ECHA note – A non confidential attachment was submitted with the comment above. FINAL IPPIC Comments on ECHA TiO2 Consultation 7-15-16.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Switzerland		BehalfOfAnOrganisation	32
Comment received				
ECHA note - Only a confidential attachment was submitted. Brief TIO2.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	JTI SA	BehalfOfAnOrganisation	33
Comment received				
JTI comments on the ANSES proposal for CLP classification of Titanium dioxide as Carcinogenic 1B (H350i) Currently titanium dioxide is not classified according to the Regulation (EC) No 1272/2008 (CLP Regulation) Annex VI. Recently, a proposal for Harmonized Classification and Labelling was submitted to European Chemicals Agency (ECHA) by the ANSES (French Agency for Food, Environmental and Occupational Health & Safety) to classify it as				

carcinogenic 1B (H350i; may cause cancer by inhalation).
In accordance with the Guidance on the Application of CLP Criteria for classification for Category 1B classification, the substance is presumed to have carcinogenic potential for humans. However, the evidence presented by ANSES is largely based on animal studies.
ANSES has based its proposal on several animal studies showing that high concentrations of pigment-grade (powdered) and ultrafine titanium dioxide dust caused respiratory tract changes including tumors in rats exposed by inhalation and intratracheal instillation (Muhle H et al., 1989; Lee KP et al., 1985, 1986; Heinrich u et al., 1995; Pott and Roller, 2005).
In the animal studies, the earliest observation upon titanium dioxide exposure was alveolar cell hyperplasia (replacement of Type I pneumocytes with Type II pneumocytes). This is a non-specific response which occurs following exposure to various materials including other 'unclassified' particulates, and it is a reversible phenomenon. After longer exposures (>12 months) to high concentrations of titanium dioxide, a frequent observation in the rat lungs were giant cell granulomas, containing minute areas of collagen fiber. This type of tissue response has mainly been reported in rats exposed to various 'unclassified' particulates and it is uncommon in man. The granuloma appears to be a tissue response to consolidated areas of dust, disintegrated macrophages, phospholipids and other cellular debris (Trochimowicz HJ et al., 1988).
The CLP regulation indicates that as part of a weight of evidence approach, some other considerations should be taken into account while assessing the overall level of concern, and this may include "(…) whether responses are in single or both sexes; whether responses are in a single species or several species; the possibility of confounding effect of excessive toxicity at test doses; mode of action and its relevance for humans (…)" etc., (CLP regulation).
In the study published by Lee et al., (1985) and cited by ANSES, authors reported increase of squamous lesions in female rats only at the highest concentration tested (250 mg/m3). A macroscopic review of the proliferative squamous lesions observed in the Lee et al., (1985) study was further published by Warheit et al., 2006 concluding that most of the lesions were diagnosed as non-neoplastic pulmonary keratin cysts.
Furthermore, Heinrich et al., (1989), also referred to by ANSES, in their study tested only female rats and no carcinogenic effect was observed in the mice. Consequently, this study would not fulfill the CLP criteria for carcinogenicity classification.
In a study reported by Muhle et al., (1991), titanium dioxide was used as a negative control dust in a two-year inhalation study with toner particles. Male and female rats were exposed (6 hr/day, 5 days/week) to 5 mg/m3 titanium dioxide (rutile form). There were no significant increases in lung tumors vs. control rats (air) exposed for up to 24 months by whole body inhalation to titanium dioxide in this study.
The International Life Sciences Institute (ILSI, 2000) Risk Science Institute addressed the numerous study reports of lung tumors in rats resulting from chronic inhalation exposures to poorly soluble, non-fibrous particles of low acute toxicity and not directly genotoxic (e.g., carbon black, coal dust, diesel soot, non-asbestiform talc, and titanium dioxide). These particulates would elicit tumors in rats when deposition overwhelms the clearance mechanisms of the lung resulting in a condition referred to as "overload." In contrast to the rat, other animal species exposed chronically to those particles have not developed lung cancer. For example, inhalation exposure of hamsters or mice to talc or titanium dioxide has not resulted in lung tumors, even though the lung particle burdens achieved in these studies were similar to or greater than those producing lung cancer in rats (Heinrich et al., 1986, 1995; NTP, 1993; Mauderly et al., 1996). Other studies indicated that the monkey lung responses to particles are different from those of the rat (Nikula et al., 1997). Additionally, studies of a human population (coal workers, mostly males) heavily exposed to particulates have not revealed any consistent evidence of increased risk of lung cancer, even though the relative mass of coal dust in the lungs of some coal workers was in the range in which some poorly soluble, non-genotoxic particles produce

cancer in rats (Mauderly et al., 1994; IARC, 1987-1997). Furthermore, rats exposed to particulates exhibit a range of squamous cell proliferative responses that do not appear to have human analogs.
It should also be noted that the studies analyzing human exposure published so far did not suggest an association between occupational exposure to titanium dioxide and an increased risk for cancer (IARC, 2010).
Few titanium dioxide-related health effects were identified in case reports (Elo et al., (1972; Yamadori et al., 1986; Moran et al., 1991; Keller et al. 1995). None of the case reports provided quantitative industrial hygiene information about workers' titanium dioxide dust exposure. Lung particle analyses indicated that workers exposed to respirable titanium dioxide had particle retention in their lungs that included titanium, silica, and other minerals sometimes years after cessation of exposure.
Most cases of tissue-deposited titanium gave a local macrophage response with associated fibrosis that was generally mild, but of variable severity at the site of deposition.
More severe reactions were observed in a few cases. The prevalence of similar histopathological responses in other titanium dioxide-exposed populations is not known.
The effects of concurrent or sequential exposure to carcinogenic particles, such as crystalline silica, nickel, and tobacco smoke, were not determined.
Five published epidemiologic studies of titanium dioxide-exposed workers represent a range of environments, from industry to population-based, and appear to be reasonably representative of worker exposures over several decades (Chen and Fayerweather, 1988; Fryzek et al., 2003; Boffetta et al., 2001, 2004; Ramanakumar et al., 2008). All the studies had methodological limitations and misclassification of exposure that could not be ruled out. Overall, they did not provide clear evidence of elevated risks of lung cancer mortality or morbidity among workers exposed to titanium dioxide dust.
In addition to the methodologic and epidemiologic limitations of the studies, they were not designed to investigate the relationship between titanium dioxide particle size and lung cancer risk, an important question for assessing the potential occupational carcinogenicity of titanium dioxide.

Conclusion
JTI disagrees with the proposal of the ANSES to classify titanium dioxide as Carcinogen 1B. The key studies selected by the ANSES are of insufficient quality and relevance for humans. Furthermore and as explained above, the human studies conducted so far neither suggested an association between occupational exposure to titanium dioxide and an increased risk for cancer nor provided evidence of a dose-response relationship.
With regard to particle overload, data suggested that this phenomenon is unlikely to occur in humans, which is in agreement with the documented epidemiology.
In conclusion, based on available scientific literature, it is JTI's view that re-classification of titanium dioxide is not necessary and that scientific evidence does not support the classification of titanium dioxide as suggested by ANSES.

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ECHA note – A non confidential attachment was submitted with the comment above. JTI comments on the ANSES proposal for CLP classification of Titanium dioxide as Carcinogenic 1B (H350i).pdf

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

Specific response to human case reports: Keller *et al.* (1995) and Elo *et al.* (1972) although not specifically summarized in the CLH report are taken into account in the dossier in the statement page 38 since they are described in the IARC monograph.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom		BehalfOfAnOrganisation	34
Comment received				
I represent and am responding on behalf of a manufacturer of decorative and technical films for speciality applications, established in the United Kingdom. We are a downstream user of titanium dioxide and are concerned about the proposal made by France for classifying this substance as a carcinogen. Our company employs 280 people, some of whom have over 40 years of service here. We have been using titanium dioxide for many years as a key component in our PVC film formulations. It is present in 95% of our current product range, at levels of up to 17%. We do not have any alternatives available which could replace this material in our product, and would not be able to achieve the required film colour, opacity, UV performance and gloss without it. As part of our workplace dust exposure control measures we carry out regular spirometry and other medical surveillance, and we are not aware of any relation between the use of titanium dioxide and the development of cancer (or any other lung diseases) by our workers. The proposed classification would therefore have a disproportionately high economic impact on our company, our employees, and also on our customers.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France	Axens SA	BehalfOfAnOrganisation	35
Comment received				
Axens supports and agrees with TDMA/TDIC position as well as VCI statement of no classification of titanium dioxide (TiO2). Our production plant in France has its own Health Department and operators (approximately 70 of them are in contact with TiO2) have a regular check-up including lung X-Ray (every 2 years). TiO2 is used since 1986 and no observation was made that would point out a connection between TiO2 exposure and cancer. Axens uses significant amount of TiO2 each year. This TiO2 is pelletized from powder to extrudates to produce a catalyst essential in Claus process. This process converts Dihydrogen Sulfur (H2S) into Sulfur and avoids H2S incineration which generates SO2 and subsequent acid rains. If TiO2 cannot be used for Claus catalyst manufacturing, there is no real suitable alternative. In current state of art, the only one would be to use Alumina (Al2O3) but, in this case, process efficiency would drop dramatically (in a range of 4 or 5) Strong investments would be required in our customers' facilities in Western Europe to maintain current production or, more probably, customers could decide to move outside the European Union leading to loss of employment in Europe.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99 and to VCI comment No. 218.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	A. Schulman Plastics BVBA	BehalfOfAnOrganisation	36

Comment received

A. Schulman (BVBA) is a leading manufacturer of Masterbatches for the plastics industry. One of our titanium dioxide using entities is A. Schulman BVBA which is located in the EU Member State Belgium. Notwithstanding the fact that as a matter of company policy we adhere the greatest importance to safety and the health and wellbeing of both our employees and the public, we feel the need to express our serious concern about ANSES' proposal for a harmonized classification and labelling of titanium dioxide as "potentially carcinogenic to humans (category 1B) / may cause cancer by inhalation (H350i)".

Titanium dioxide is widely used in the plastics industry and offers extraordinary properties like extreme light fastness and high refractive index and light scattering. It has the highest opacity among all white pigments and provides excellent brightening capacity. These properties make it a unique pigment for all kind of plastics applications. Its properties are not matched by any other white pigment. To the best of our knowledge the TDMA (Titanium Dioxide Manufacturers Association) has adequately researched the potential health hazards of titanium dioxide and we therefore fully support the comments provided by the TDMA.

A classification as proposed by ANSES would have serious consequences for the whole plastics industry value chain. Considerable obligations, restrictions, or bans would impact our industry significantly. Many of our businesses (film, foil and packaging) are built around the special features of this pigment that is bound in a polymer matrix and not freely available as dust. We therefore request that ECHA exercises caution and very carefully considers all available toxicological and epidemiological evidence that strongly supports the conclusion that the proposed classification and labelling would be inappropriate.

Dossier Submitter's Response

See points 1 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Glass Alliance Europe	BehalfOfAnOrganisation	37

Comment received

ECHA note - Only a non confidential attachment was submitted.
TiO2 - GAE comments to ECHA consultation.pdf

Dossier Submitter's Response

See points 1, 2 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece		BehalfOfAnOrganisation	38
Comment received				
'I represent the company <confidential> established in the EU Member State GREECE and respond on behalf of that company. We are a formulator of coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 100 people. We have been using this substance for 60 years. As we successfully manage the workplace exposures of dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public as also Ecolabel paints) and to our company. ECHA note – A non confidential attachment was submitted with the comment above. 2016-07-15 Public Consultation particip. (confidential) comm.pdf				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	EFfCI - The European Federation for Cosmetic Ingredients	BehalfOfAnOrganisation	39
Comment received				
EFfCI (The European Federation for Cosmetic Ingredients) welcomes the opportunity to contribute to the Public Consultation on the CLH Proposal for Titanium Dioxide (all forms) as Carcinogen 1B (by inhalation). In this submission, we provide 1. Information about EFfCI, the Cosmetic Supplier Industry as well as the importance of Titanium Dioxide as a cosmetic ingredient 2. Position concerning the toxicological /scientific aspects of the proposed classification 3. Impact of a Carc 1B classification to the cosmetics supplier industry 4. Conclusion Information about EFfCI, Cosmetic Supplier Industry and various functions of Titanium Dioxide in Cosmetic Products EFfCI is the European trade association representing the interests of the cosmetics ingredient supplier industry. EFfCI represents more than 100 ingredients companies throughout the EU and more than 80 % of the cosmetics ingredient market in the EU. The vast majority of the member companies are SME'S For more information about "EFfCI", please consult our website: http://effci.com/ Within the value chain for cosmetic finished products the cosmetics ingredient industry stands at the very beginning. Titanium Dioxide is offered in specifically developed qualities and combinations adapted to the specific uses of cosmetics, e.g. as UV filter and				

colorant.

In cosmetics, Titanium Dioxide is widely used as colorant, as opacifier or as UV Filter and is chosen due to its efficacy and performance. Titanium dioxide is regulated under the European Cosmetic Products Regulation (EU CPR 1223/2009) as a cosmetic colorant (CI 77891, Annex IV) approved for all cosmetic products without any restrictions and as a UV filter (Annex VI) with a maximum concentration of up to 25%. Titanium Dioxide is one of the very few globally approved UV Filters / Sunscreen actives which is of relevance for global formulations.

The use of TiO2 in cosmetic products is longstanding and an extensive toxicological data set is available. The safety of TiO2 materials has been acknowledged by a wide range of scientific and regulatory bodies throughout the world (e.g. EU EFSA, US FDA), resulting in their safe uses in various products including food products. For Cosmetic Products, the SCCS has reviewed and concluded on the safety of Titanium Dioxide on various occasions, latest in their opinion SCCS/1516/13 of 22/07/2013 (Revision of 22 April 2014) on Titanium Dioxide (nano). It is to be noted that the SCCS has considered inhalation exposure in this review.

Especially for the use as colorant and UV filter there are no alternatives which are either approved under the Cosmetics Regulation nor are able to replace Titanium Dioxide for these uses.

Position concerning the toxicological /scientific aspects of the proposed classification

EFfCI fully supports the comprehensive scientific statement by TDMA / TDIC and the positions submitted by the German VCI and that of Cosmetics Europe – the latter addressing the specific parts concerning the use of Titanium Dioxide in cosmetic products.

Impact of a CMR 1B classification in specific concerning cosmetic products and in general

A classification of TiO2 as CMR 1B would automatically result in a ban of TiO2 for its use in cosmetic products. This follows from the European Cosmetic Products Regulation (EU CPR) which states in Article 15.2 that "the use in cosmetic products of substances classified as CMR category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008 (CLP) shall be prohibited". Exemptions to the CMR 1A and 1B ban are possible, however they can only be granted in very exceptional cases, when a series of stringent conditions are fulfilled (no alternatives, food compliance, safety dossier, specific uses…). This process– if selectable – does not provide the needed continuity for the industry and needs several months up to years to be clarified - if possible at all. Finished cosmetic products (currently in the market) are not compliant to legislation any longer and have to be recalled, formulations revised. A reactivation of the substance has to overcome numerous hurdles from a regulatory and market perspective.

In addition a number of automatic legal consequences will result from a CMR 1B classification of TiO2.
• During manufacture of TiO2 additional protection measures are required. Whereas restrictions on dust exposure in plants already exist on national level a number of EU Regulations on hazardous substances have to be followed in addition.
• Measures on personal protection and medical surveillance have to be heavily extended.
• The waste management has to aligned to the handling with hazardous substances.

Conclusion

EFfCI concludes that no human evidence for increased lung cancer risk exists. This is well acknowledged within the scientific community and is further supported by the existing epidemiological evidence from well-conducted studies that showed no causal relationship between workers exposure to TiO2 and the development of lung tumors.

EFfCI is deeply concerned about the proposal for classifying titanium dioxide as carcinogen (cat. 1B).
Taking into account on one hand the scientific point of view not showing a comprehensible reasoning for the proposed classification and on the other hand the importance of titanium dioxide in cosmetic products, i.e. the economic impact for our industry as well as for our downstream users, EFfCI agrees to and fully supports the TDMA/TDIC as well as the VCI position "no classification of titanium dioxide" – these industry associations provide in their comments comprehensive reasoning
why the classification of titanium dioxide as carcinogen cat. 1b is considered to be not adequate.

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece	HELLENIC ASSOCIATION OF CHEMICAL INDUSTRIS	BehalfOfAnOrganisation	40

Comment received

Our Assotiation represents the Greek based chemical industry . Many of ourmembers are using titanium oxide in their products namely :
-Coatings (deco, industrial, vehicle refinishing etc.)
• Printing inks
-Master batches
-Pharmacuticals and cosmetics etc

A harmonised classification as potentially carcinogenic would have far-reaching impacts on many legal provisions (e.g. on the safety of industrial plants and environmental and consumer protection). Comprehensive obligations and bans or restrictions would be the automatic consequence, without any further examination of whether the use of titanium dioxide in real life poses any risks. For example, a classification of titanium dioxide as potentially carcinogenic according to Annex XVII points 28 and 30 of the REACH Regulation would result in a ban for the sale of paints and coatings to private final consumers (e.g. in do-it-yourself stores). Moreover, titanium dioxide would need to be substituted – irrespective of whether replacement substances of equal quality are available

Dossier Submitter's Response

See point 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France		BehalfOfAnOrganisation	41
Comment received				
Impact of a CMR IB classification on cosmetic products We have great concerns on negative implications for cosmetic industry caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter in sunscreen products cannot be put in use in market. Based upon the reasons mentioned in the specific comments, we concerned about the sentence: "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B-H350i", is lack of sound scientific evidence. (4.1.6, page 69) When IARC classified TiO2 in the Group 2B "possibly carcinogenic to humans", it didn't have any negative impact on cosmetic industry since IARC does not limit the use of TiO2 as cosmetic ingredients. However, if TiO2 is classified as Carc. Cat 1B-H350i by CLP regulation, TiO2 cannot be used in cosmetics according to Article 15 of the Cosmetics Regulation 1223/2009, "the use in cosmetic products of substances classified as CMR substances (substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity), of category 1A or 1B under Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures. Though such substances may be used in cosmetic products by way of exception where all of the conditions addressed in the article are fulfilled, none of substances have been exempted by fulfilling them all to date. Thus, we would like to request the authorities to reconsider the classification of TiO2 based on more realistic exposure simulation since we believe TiO2 does not show carcinogenic potential under normal and foreseeable misuse conditions of cosmetics containing TiO2.				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece	HELLENIC COATING ASSOTIATION	BehalfOfAnOrganisation	42
Comment received				
The proposed classification and labelling of titanium dioxide as "presumed to have cancerogenic potential for humans" is not justified from the toxicological perspective. Such classification would have serious negative impacts on the European and Greek markets for paints, coatings and printing inks. Our Assotiation counts almost 20 enterprises, SMEs in their majority. They are using in their products almost 3000 tones per year. . Titanium dioxide is used in many fields of paints, coatings and printing inks, e.g. in • Decorative coatings mainly • Plaster and putty • Anti-corrosion coatings • Wood varnishes and paints • Industrial coatings • Printing inks • Vehicle refinishing coatings • Powder coatings				

• Traditional organic paints • UV-curing coatings Many deco products that contain titanium oxide are awarded with the eco label scheme. Titanium dioxide is known as an extremely lightfast, has a high refractive index and a very high light scattering capacity. From the coloristic perspective it has, therefore, the highest opacity among all white pigments as well as an excellent brightening capacity vis-à-vis coloured media. Furthermore, titanium dioxide is thermally stable, not combustible, nearly insoluble in water, and weather and UV resistant.2 For paints, coatings and printing inks, there are hardly any alternatives to titanium dioxide. Other raw materials (e.g. calcium carbonate, zinc oxide and zinc sulphide) are usually of inferior quality regarding stability and opacity, brightness (gloss) and abrasion resistance. In addition, a substitution of titanium dioxide would not change the given situation since the carcinogenic effect in animal testing is not substance-specific but characteristic of dusts and dust exposure can be expected also in the processing of alternative substances. Due to the inferior quality and the higher costs of replacement substances, considerable damage to the national economy must be expected. Our member companies also fear that the discussion about titanium dioxide will cause uncertainty among customers and, consequently, lead to a reserved buying behaviour. A harmonised classification as potentially carcinogenic would have far-reaching impacts on many legal provisions (e.g. on the safety of industrial plants and environmental and consumer protection). Comprehensive obligations and bans or restrictions would be the automatic consequence, without any further examination of whether the use of titanium dioxide in real life poses any risks. For example, a classification of titanium dioxide as potentially carcinogenic according to Annex XVII points 28 and 30 of the REACH Regulation would result in a ban for the sale of paints and coatings to private final consumers (e.g. in do-it-yourself stores). Conclusion: From the toxicological perspective, a classification of titanium dioxide as potentially carcinogenic is neither necessary nor justified (see specific comments below). Given the automatic link to regulatory requirements, such a classification would have serious negative effects on the market for paints, coatings and printing inks without contributing to the protection of health and the environment.
Dossier Submitter's Response
See point 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	AUXICOLOR S.L.	BehalfOfAnOrganisation	43
Comment received				
Dears, we just would like to point that Titanium dioxide has been used in our company in hight amonut quantity for 40 years without toxical effects. For our company is the most important raw material, as most printing pastes for textile printing contain it.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Norway	Jotun A/S	BehalfOfAnOrganisation	44
Comment received				
As a downstream user/ handler of Ti-dioxide powder Jotun A/S has not had any health issues with this or any other "low toxicity low solubility (LTLS)" materials. There are no alternatives to Ti-dioxide. If Ti-dioxide is, in our opinion, incorrectly classified as carcinogenic it will have big consequences (see attachment) not only for the use of Ti-dioxide but maybe for all the "LTLS"-materials (read-across?). Jotun A/S supports that legislation puts strict restrictions on CMRs when proven true. In the case of Ti-dioxide Jotun A/S believes this is not proven. Hazard classification should be based on hazard characterisation taken into account aspects such as mode of action, toxicokinetic and -dynamic, dose response and relevance to humans. The carcinogenic effect is due to lung overload observed in rats only and is of no relevance to humans. ECHA note – A non confidential attachment was submitted with the comment above. Consequence of a TiO2 Ban.docx				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	FCIO - BG Lack- und Anstrichindustrie	BehalfOfAnOrganisation	45
Comment received				
Wir, als Distributor, vertreiben seit mehr als 20 Jahren Titandioxid für den österreichischen Markt. Die Anwendungen unserer Kunden lagen und liegen im Lack- und Anstrichbereich als auch in den Bereichen Kunststoff und Kautschuk. Während dieser mehr als 20 Jahre haben wir über unser Lager geschätzt 4.000 to Titandioxid bewegt.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Poland	Farby KABE Polska Sp.z o.o.	BehalfOfAnOrganisation	46
Comment received				
We are the leading producer of plasters and paints with over 20 years of market experience. In all this time we have never had information of health (cancer) problems from our customers or workers because of the TiO2 used in our products. Furthermore human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. Titanium dioxide is one of our strategic raw-materials and in this moment it is not possible to substitute it by any other material. Due to its properties TiO2 is unique filer and UV absorber. We are convinced that TiO2 provides many benefits to our products. TiO2 has been produced for nearly the century. As well known TiO2 is used in paints and coatings, plastics, paper, building materials, cosmetics, pharmaceuticals, foods and many				

other commercial products. It's the world's primary pigment for providing whiteness, brightness, opacity and UV stability. It's everywhere around us. If it were so dangerous, we would have world-wide cancer epidemic. But we do not. Therefore we fully support the position provided by TDMA that no classification for TiO2 can be justified .
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Poland	Grupa Azoty Zaklady Chemiczne "Police" SA	BehalfOfAnOrganisation	47

Comment received

Titanium dioxide pigments have been produced by Grupa Azoty Zakłady Chemiczne Police SA since 1977. No special case of cancer related to titanium dioxide has been observed during almost four decades of our activity. In our production practice we are following the Polish regulations with exposure limits for titanium dioxide, i.e. 10mg/m3 of inhalable dust. Measurements of the titanium dioxide concentration in the work environment are made regularly at our production site and the recorded dust concentrations of inhalable fraction of titanium oxide are below exposure limits. Moreover our workers prophylactically are equipped in inhalation masks type FFP2 acc. to EN 149.

Furthermore our downstream users are very well informed about physical and chemical properties of our pigments, including information about 2B classification by IARC ("Possibly carcinogenic to humans"). All details referring to appropriate safe handling are included in our Safety Data Sheets (SDS).
Never have we heard information from our customers of health (cancer) problems caused by use of TiO2 pigments.

Some researches, being in the minority, evaluated TiO2 as "possibly carcinogenic to humans" on studies in rats. However, it is generally recognized that the rats are uniquely sensitive to the effects of "lung overload" which is not observed in other species including humans. On the other hand many published epidemiological studies investigating titanium dioxide (TiO2) production workers confirmed no correlation between TiO2 lifetime work exposures and lung cancer risk.

Based on existing safety information, it can be concluded that there are not sufficient scientific and human data to classify pigmentary titanium dioxide as a carcinogenic substance (Carc. 1B – H350i)! Human data does not suggest an association between occupational exposure to TiO2 and risk for cancer (CLH report page 8).

If the proposed classification will be agreed many branches will undergo serious problems, because globally produced titanium dioxide pigments are used in a lot of final applications (the main are paints & inks, plastics, paper, rubber, adhesives, sealants, ceramics, cosmetics) and there are no suitable substitute raw materials available for them.

Therefore the downstream users of titanium dioxide express their concern that the

classification of TiO2 as a carcinogenic substance (Carc. 1B – H350i) shall significantly complicate the utilization of unquestionably the most important white pigment. Summarizing, we fully support the position provided by TDIC and TDMA, which is no classification and labelling of TiO2. ECHA note – A non confidential attachment was submitted with the comment above. Police's opinion - Polish version.pdf
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		BehalfOfAnOrganisation	48
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO carcinogen classification of TiO2. Our company is a substantial user of TiO2 with a long history of manufacturing TiO2 containing products supplied into consumer applications. Substantial product quantities have been supplied over many years without any reported or recorded issues associated with the use of TiO2. The proposed classification would accordingly be expected to have an impact on our business. The comments on the proposal are covered in our support for the information provided by TDIC and TDMA.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	Johnson Matthey Catalysts (Germany) GmbH	BehalfOfAnOrganisation	49
Comment received				
Johnson Matthey Catalysts (Germany) GmbH fully supports and agrees with the response submitted by Titanium Dioxide Manufacturers Association (TDMA) and Titanium Dioxide Industry Consortium (TDIC); as well as the position submitted by Verbrand Der Chemischen Industrie (VCI) which summarise: (1) the significant amounts of scientific evidence supporting the argument that inter-species extrapolation of long overload effects from rats to humans are not justified; (2) the complete absence of epidemiological evidence of poorly soluble particle-induced lung cancer in titanium dioxide workers, even in clearly particle-overloaded lungs; (3) the absence of direct evidence of nanoparticles binding to DNA; (4) the existing mechanisms in place (e.g. TRGS 559 "Mineral dust") which ensure a high level of worker protection is in place for this substance, and; (5) the current applications and limited availability of safer and more sustainable alternatives.				

In the case of Johnson Matthey Catalysts (Germany) GmbH, titanium dioxide is a key component in our emission catalysts which play critical roles in the reduction of emissions of pollutants such as nitrogen oxides, carbon monoxide and volatile organic compounds in stationary (e.g. coal-fired power plants and gas turbines) and road- and non-road transport (e.g. diesel engines) applications. In addition, Johnson Matthey's titania-based Selective Catalytic Reduction (SCR) catalysts not only remove Nitrogen Oxides but simultaneously enable improvements in the fuel efficiency of heavy duty trucks, buses and non-road mobile machinery, which leads to significant reductions in CO2 emissions.

The scientifically unjustified proposal to classify titanium dioxide as carcinogenic category 1B would be burdensome to our company and detrimental to the perception of our products which provide significant benefits to the environment.

Dossier Submitter's Response
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	NADICO Technologie GmbH	BehalfOfAnOrganisation	50

Comment received

As a manufacturer of photocatalytically active coatings we are using titanium dioxide as raw material for our products. Therefore we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen.

(1) Our company NADICO Technologie GmbH (NADICO) is established in the EU member State Germany and currently employs 19 people.

I am responding on behalf of NADICO as the responsible officer of the legal department.

(2) We manufacture and supply water-based dispersions containing nanoscale TiO2. Those dispersions are used to produce photocatalytically active coatings which are used to

– clear the air (e.g. from nitric oxides NOx) (outdoor use),
– keep window panes, façades, roofs, other building components and PV modules clean (outdoor use),
– protect façades, roofs, other building components and PV modules against algae and mould (outdoor use),
– clear the air from VOC, formaldehyde and other harmful gases (indoor use),
– clear the air from unpleasant odours (indoor use),
– protect surfaces against germs and mould (indoor use).

Photocatalysis is (to our knowledge) the only technology which is able to decompose harmful gases and solids to harmless compounds without adverse environmental effects.

(3) Titanium dioxide is the key material of our products. The proposed classification would affect all our products and would lead to the complete shutting down of our company. Moreover, this would be disproportionate as it would have highly negative economic impact to the whole market of photocatalytically active coatings in Europe, compared to

minimal risk reduction to the consumer.

To the contrary, our photocatalytically active products are replaceable only by products with mainly negative impacts on environment and economy:

– as to the air clearing properties:
replaceable by air clearing devices; their disadvantages are costs for acquisition, for electricity and for filter media, moreover, operating noise and waste production (e.g. used filter media);

– as to the self-cleaning properties:
replaceable by cleaning materials and frequent cleaning efforts, with the disadvantages of running costs and of environmental pollution;

– as to the prevention against algae and mould:
replaceable by several biozides with harmful components, with the disadvantages of costs for application and maintenance and of environmental pollution.

(4) We and our partner companies (who manufacture dispersions on our behalf) have been using titanium dioxide in powder form for many years by successfully managing the workplace exposures of dust by a variety of permanent measures. There has never been any indication to the development of cancer by the workers.

Moreover, in our products titanium dioxide is bound in a polymer matrix and thus not exposing any health hazards to our customers and to all consumers.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Poland	FFiL Śnieżka S.A.	BehalfOfAnOrganisation	51

Comment received
I represent the company ŚNIEŻKA PLC has established in the EU Member State. We are a formulator of paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs about 800 people and we have been using this substance for 30 years. So far we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market and to our company.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	Treibacher Industrie AG	BehalfOfAnOrganisation	52
Comment received				
We are a manufacturer of environment catalyst materials and materials for hard metal applications (e.g. cutting tools, drills…) using titanium dioxide as raw material for our products. The company Treibacher Industrie AG is established in the EU Member State Austria. I respond on behalf of that company and we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs approx. 800 people. We have been using titanium dioxide powders for many years by successfully managing the workplace exposures of dust through permanent measures e.g. housings, filtration or controlled air exchange in combination with appropriate personal protective equipment. Based on this 50 years experience of using titanium dioxide we are not aware of any relation to the development of cancer by our workers. Titanium dioxide is a key material to manufacture our products. The proposed classification would also affect all chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our titanium dioxide products have to face a direct or indirect loss in sales either through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	BAH German Medicines Manufacturers Association	BehalfOfAnOrganisation	53
Comment received				
See uploaded Attachement! ECHA note – A non confidential attachment was submitted with the comment above. TiO2 Stellungnahme BAH 2016_07_15.docx				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		MemberState	54
Comment received				

Substance Identity
According to the title page of the report the CLH proposal covers the substance Titanium dioxide (EC Number: 236-675-5, CAS Number: 13463-67-7). The same substance identifiers are given in Part B, section 1.1 and 1.2 of the CLH report. Deviating from this in Part A, section 1.1 three substances are listed: Titanium dioxide (CAS: 13463-67-7, EC: 236-675-5), Anatase (TiO2) (CAS: 1317-70-0, EC: 215-280-1) and Rutile (TiO2) (CAS: 1317-80-2, EC: 215-282-2).

Furthermore, in Part A, section 1.1 it is mentioned that
"the proposed scope for the Annex VI entry is: Titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies".

In addition, in Part A, section 2.2 of the report it is stated that
"all possible crystal modifications, morphologies and surface chemistries in all possible combinations of TiO2 are […] covered by this CLH dossier."

Since the scope of the CLH proposal should be completely clear, the information on the identity of the substance(s) covered by the dossier have to be consistent through the whole report. From our point of view the title of the report should already include the scope "Titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies" and all corresponding substances and identifiers (CAS and EC numbers) should be listed. Furthermore, the information on the substance identity has to be consistent.

We recommend to review all substance identity relevant sections of the CLH report and to adapt them accordingly. Moreover, it is known that titanium dioxide may also appear in fibrous form including rigid fibres which have the so-called WHO dimension. Such fibres would be assumed to have an asbestos-like action. The carcinogenicity of rigid biodurable WHO fibres is orders of magnitude higher than for granular material. It should be made clear in the proposal that WHO morphologies of titanium dioxide are excluded from the CLH proposal.

The critical effect, lung carcinogenicity, is caused by titanium dioxide in respirable form (roughly particles smaller than 10 µm) only. Such qualification is normally not expressed in substance entries in the CLP regulation. This should be emphasized more prominently in the CLH proposal to initiate a discussion on this point.

In Part A, section 2.2 of the CLH report the following sentence is given:
"Titanium dioxide can also be modified by using various coatings (including aluminum oxide, silicon dioxide, calcium salts…) or dopant agents to enhance or maintain its properties."
Keeping in mind that undoped and (differently) doped substances have deviating substance identities such substances have to be considered separately. In order to cover doped forms of titanium dioxide in the CLH proposal as well, they have to be clearly addressed and mentioned in the substance identity sections.

Carcinogenicity
The CLH proposal and the weight of evidence related to the primary pathogenic mechanism leading to carcinogenicity is plausible for dust-forming particles, including agglomerating nanoparticles.

Dossier Submitter's Response
See point 1 of the attachment to the RCOM. In addition, for the specific comment on TiO_2 under fibrous form, the proposed scope includes all morphologies of TiO_2, including fiber-like shapes. Concerning doped titanium dioxide, this would not be considered the same substance as non-doped titanium dioxide, unless the purpose of the doping is to act as a stabiliser.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Denmark		BehalfOfAnOrganisation	55
Comment received				
Our company has used TiO2 in the production of coatings for more than a century, and we are surprised that the substance is now being considered carcinogenic. We would not have guessed, because in our experience there are no such indications. As a member of CEPE we are aware of the CEPE and TMDA/TDI position to proposal, and we do support the scientific comments they'll make to the CLH proposal. Also, we do find that ECHA should ask the registrants of TiO2 for more detailed information instead of making this CLH proposal covering all forms of TiO2. Finally, we do miss classification options for: TiO2, non-respirable particles, dry or wetted TiO2 in a matrix, where particles are not directly available for biological uptake.				
Dossier Submitter's Response				
See points 1 and 2 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Cathay Industries Europe nv	BehalfOfAnOrganisation	56
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Celanese	BehalfOfAnOrganisation	57
Comment received				
Celanese comment to the proposed classification of titanium dioxide (potentially carcinogenic to humans" (category 1B) / "may cause cancer by inhalation" (H350i)). Celanese, a major manufacturer of plastic compounds and acetate tows would be significantly and negatively impacted by the proposed classification. It would require to classify many products of Celanese that currently are considered non-hazardous. The consequence of such classification in the next level of the supply chain results in				

classification of consumer products which could then no longer be sold into applications for the general public. Consumer products then will fall under the ban of the sale to the general public according to the REACH regulation (EC) 1907/2006, Annex XVII point 28. There is currently no adequate substitute to TiO2 as a white pigment in plastic materials and we anticipate a significant market loss if TiO2 was classified. Many applications could disappear where plastics parts are used safely and reliably. The proposal is based on results from "lung overload" studies in rats which should not be transferred to humans. Regulation EC/1272/2008 and related guidance document do not provide justification either. ECHA "Guidance on the Application of the CLP criteria" "3.9.2.5.3. Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e)) In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans. […] Lung Overload The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate." The risk associated with dusts at the workplace is well regulated in various (European) countries, e.g. by Germany with an entry for dust in TRGS 900. We fully support the arguments against classification expressed by VCI in their statement made on July 4th, 2016. We also support the proposal made by VCI to establish a binding occupational exposure limit value for titanium dioxide dusts to protect workers on an EU level.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to VCI comment No. 218.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	ASCER	BehalfOfAnOrganisation	58
Comment received				
ECHA note - Only a non confidential attachment was submitted. ASCER statement on the proposal for a harmonized classification of Titanium dioxide.docx				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Glasindustrie e.V.	BehalfOfAnOrganisation	59
Comment received				
Titanium dioxide is used by some companies from the flat glass and special glass sector. Altogether, more than 2.000 t are used in the glass industry each year. It is either used				

for special glass in the glass batch itself or for coating of flat glass. For some special glass applications, following intense research to substitute lead oxide, new formulations are used in which TiO2 is used instead of PbO. With regard to special glass, depending on the application, the concentration of titanium expressed as TiO2 in glasses varies from less than 1 % to about 25 % (Best Available Techniques Refer-ence Document (BREF) for the manufacture of glass, table 2, p. 67). With regard to the use of TiO2 in glass articles via coatings, paints and decorating inks, it ranges from 0,01 % to 0,02 %.

Glass is an inorganic material obtained from different inorganic raw materials which react at high temperature. During this process, the raw materials form a new random network. The chemical elements are incorporated via strong new chemical bonds and become an integral part of the glass' three-dimensional structure. By convention the glass composition is generally expressed as oxides of the constituent elements (SiO2, Na2O, K2O etc.). There is no titanium dioxide in the glass products (except for self-cleaning coatings where titanium dioxide is present as a very thin layer on the sur-face), but titanium ions are present in the glass matrix.

There are no possibilities for substitution as no other substance has the same positive effects on glass. It has a significant impact on the chemical and physical resistance of the glasses, the light refraction, UV-absorption, weight/density, crystallisation behav-iour, expansion behaviour, mechanical strength and for window glass in buildings and in cars sun protection properties, good light, anti-reflection and energy performance.

We disagree with the classification and labelling of titanium dioxide as carcinogen 1B by inhalation (H350 i) as titanium dioxide has been used safely for many years. To our knowledge, there is no data suggesting a causal link between lung cancer and the use of TiO2 in the glass industry.

We support the comments submitted by Glass Alliance Europe (GAE) and the Titani-um Dioxide Manufacturers Association (TDMY) with the Titanium Dioxide Industry Consortium (TDIC).

Dossier Submitter's Response
See points 1, 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Owens Corning Veil Netherlands B.V.	BehalfOfAnOrganisation	60

Comment received

Our company uses Titanium dioxide in the coatings of non woven veil products for wall covering applications.
TiO2 is delivered and used as a water slurry added in the coating.
Consequently, there is limited, if any, exposure to TiO2 within our manufacturing operations and within our downstream supply chain and end consumers.
No health issue related to exposure to TiO2 has been reported to us.
However, TiO2 classification as Carc. 1B would have significant detrimental impact on our company:
- This classification would lead to additional costs related to the general requirements applicable to any CMR substances (substitution, closed system, medical

surveillance, etc…) - It would also very likely trigger customer requests for phasing out TiO2 products while there is no known safer and technically/economically available alternative. In summary, Carc. 1B classification would entail undue disproportionate additional costs and potential loss of business with no tangible human health and/or environmental benefit.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Estonia		BehalfOfAnOrganisation	61
Comment received				
I represent a downstream user / formulator of paints. We are very concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. The safety of our workers is very important issue for us, and we do our best to avoid any dust in the working air. We have been using the raw-material at least 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. As TiO2 is one of the key raw-materials of any consumer, professional or industrial paint, the classification would also affect to our products. As the health hazard is related to the inhalation of dust, the downstream legislation due to this new classification is not justified. All finished liquid products (and all materials where TiO2 is bound to a matrix) based on the TiO2 would be affected by this new classification. The proposed classification would remove the white decorative products from the consumer market, and make it more difficult for the professionals and industry to use paints, and thus have high economic impact to our market and to our company. The market today demands for white paints and good hiding power, and in this respect TiO2 is unique – there is no direct replacement for TiO2 with similar technical properties.				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	Neogene Paints Limited	BehalfOfAnOrganisation	62
Comment received				
I represent the Neogene group of companies established in 1934 in the EU Member State of the United Kingdom and respond on behalf of that company. We are a formulator of paints and surface coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 18 people. We have been using this substance for over 80 years. As we successfully manage the workplace exposures of dust (refer to aspect 2 detailed in page 1), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general				

public, refer to aspect 3, detailed in page 1) and to our company' (refer to aspect 4, detailed in page 1).
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	Asociacion Nacional de Importadores de Materias Primas para Uso Cerámico (AIMPR)	BehalfOfAnOrganisation	63
Comment received				
The proposed classification and labeling for titanium dioxide by the French MSCA would have serious and disproportionately negative impacts on the European market. Titanium dioxide is one of the raw material commonly imported by our companies members. It is worth pointing out that titanium dioxide is a raw material that is used even by SMEs, e.g. manufacturer of complex inorganic pigments, frits and preparations, in quantities up to several hundred thousand tons per year each. It is used as starting material for the synthesis of important inorganic coloured pigments (e.g. with rutile type structure). Here, titanium dioxide is fully converted during the production process. As a structure-giving component, titanium dioxide is the indispensable basis for the manufacture of these colour pigments. Titanium dioxide are firstly used in industrial applications. ECHA note – A non confidential attachment was submitted with the comment above. 14072016_AIMPR inpult CLH Titanium dioxide-final .pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	EMO - European Mortar Industry Organisation	BehalfOfAnOrganisation	64
Comment received				
EMO, the European Mortar Industry Organisation, represents manufacturers of factory made mortars from 12 EU and EFTA Member States. TIO2 is being used in renders, plasters and special smoothing mortars for surface finishing. TIO2 is the most important white pigment for the industry and there is no adequate replacement for it. A classification as carcinogen would therefore have severe negative impacts on our industry.				

The classification of TiO2 is in our understanding highly questionable as the CLH report itself fails to present clear and unambiguous scientific evidence for a risk of cancer that is specifically related to TiO2 exposure. Our main objection is based on the transferal of laboratory results on rats to humans, especially as the rats were exposed to very high concentrations of TiO2 dust that resulted in "lung overload" effects. Such "lung overload effects" are not specifically related to TiO2 but can be caused by a large number of other types of dust. We understand that for this and other reasons there is clear guidance – if not a common understanding to not transfer results from "lung overload" studies on rats to humans.

To our knowledge there are also no known cases of cancer that are unequivocally related to TiO2 inhalation. This is supported by investigations on humans to which the filed CLH report refers, which "do not suggest an association between occupational exposure to TiO2 and risk of cancer".

By proposing to the European Chemicals Agency (ECHA) to classify TiO2 as a category 1B carcinogen based on the filed CLH report, the guidance on transferal of results from "lung overload" studies on rats to humans is obviously being ignored while the lack of human evidence is being discarded on the grounds of "methodological limitations" of respective studies and a debatable level of exposure. However, in respect to the latter argument one has to note and consider that while specific TiO2 occupational exposure limits do not exist, general requirements to the limitation of inhalable resp. respirable dust apply.

Obviously we are surprised how some results were interpreted/weight and used to substantiate the proposal and others discarded. Consequently, we are highly concerned that on the basis of such an interpretation and use of results a decision could be taken that would have a severe negative impact on the industry, with potential consequences beyond the uses that would produce inhalable TiO2.

EMO therefore fully supports the positons and comments of the German Chemical Industry Association (VCI) as wells as the Titanium Dioxide Manufacturers Association (TDMA) and the Titanium Dioxide Industry Consortium (TDIC).

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99 and to VCI comment No. 218.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	Asociacion Nacional de Fabricantes de Fritas, Esmaltes y Colores Cerámicos (ANFFECC)	BehalfOfAnOrganisation	65

Comment received

The proposed classification and labeling for titanium dioxide by the French MSCA would have serious and disproportionately negative impacts on the European market regarding the products manufactured by our member companies.

Titanium dioxide is commonly used in the frits and inorganic pigments sector in Spain. Within our industry, titanium dioxide is one of the most prominent raw materials.

It is worth pointing out that titanium dioxide is a raw material that is used even by SMEs, e.g. manufacturer of complex inorganic pigments, frits and preparations, in quantities up to several hundred thousand tons per year each.

It is used as starting material for the synthesis of important inorganic coloured pigments (e.g. with rutile type structure). Here, titanium dioxide is fully converted during the production process. As a structure-giving component, titanium dioxide is the indispensable basis for the manufacture of these colour pigments.

These complex inorganic pigments are used mainly in ceramic sector and also in other surface applications like plastics, coatings…

TiO2 is mainly used as an opacifier in the production of frits, glazes and enamels. Its use is essential in order to obtain very opaque white frits for the production of glazes and enamels. It is also necessary to obtain no water mark opaque engobes, used in the production of ceramic products.

Typical concentrations of titanium dioxide in complex inorganic pigments are between 1 and nearly 100%.
The typical concentration range in frits is between 3 – 20 % of TiO2.

The TiO2 concentration in final mixture strongly depends on the application.

Inorganic Pigments, frits and preparations containing Titanium dioxide are firstly used in industrial applications.

ECHA note – A non confidential attachment was submitted with the comment above. 14072016_ANFFECC inpult CLH Titanium dioxide-final .pdf

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	Producers and Importers of Frits, E.E.I.G.	BehalfOfAnOrganisation	66

Comment received

The proposed classification and labeling for titanium dioxide by the French MSCA would have serious and disproportionately negative impacts on the European market regarding the products manufactured by our member companies.

Frit is a substance, result of a mixture of inorganic chemical substances produced by rapidly quenching a molten, complex combination of materials, confining the chemical substances thus manufactured as nonmigratory components of glassy solid flakes or granules. Therefore the starting raw material TiO2 is bound in a vitreous matrix and thus not freely available.

Titanium dioxide is commonly used in the frit sector in Europe. Within our industry (SMEs concentrate the major number of European companies), titanium dioxide is one of the most prominent raw materials; indeed, the production of frits and preparations with Ti-

content cover quantities up to several thousands Tn/year.
TiO2 is mainly used as an opacifier in the production of frits, glazes and enamels. Its use is essential in order to obtain very opaque white frits for the production of glazes and enamels. It is also necessary to obtain no water mark opaque engobes, used in the production of ceramic products.

The typical concentration range in frits is between 3 – 20 % of TiO2.

The TiO2 concentration in final mixture strongly depends on the application.

Frits and preparations containing Titanium dioxide are firstly used in industrial applications.

ECHA note – A non confidential attachment was submitted with the comment above. 14072016_FC inpult CLH Titanium dioxide-final .pdf

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		BehalfOfAnOrganisation	67
Comment received				
TiO2 is an essential ingredient in all kinds of road marking materials. Only with TiO2 retroreflecion of headlights beams can be performed and road markings can be seen at night. TiO2 also contributes to day light visibility of road markings. Road markings are essential for road safety. Without TiO2 road markings would not be possible.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	Chemical Industries Association	BehalfOfAnOrganisation	68
Comment received				

Titanium Dioxide (TiO2) is a major industry in the EU with some 300,000 tonnes per annum being manufactured in the UK alone. The application of TiO2 can be linked to a wide range of products requiring opacity or whitening function such as paints, plastics, inks, paper, food, cosmetics, and pharmaceuticals.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES), has submitted a proposal to the European Chemicals Agency (ECHA) to classify TiO2 as a category 1B carcinogen with the accompanying Hazard Statement H350i: May cause cancer by inhalation.

The Chemical Industries Association (CIA) would like to take this opportunity to provide a number of observations on the CLH report submitted to RAC. We believe that the approach taken on TiO2 goes against the current scientific thinking on this substance and

others exhibiting similar properties. As a consequence CIA does not support the rationale behind the CLH proposal for the following reasons:

1. Relevance of 'lung overload' studies
The proposal put forward by Anses is primarily based on 'lung overload' studies in rats which were exposed to significantly higher levels of TiO2 than those present in normal foreseeable conditions . Although these studies show tumour formation in the lungs of rats, this is a phenomenon specific to rats and therefore cannot be used to conclude carcinogencity in humans. This is substantiated in guidance issued by several bodies including ECHA1, OECD2 and the conclusions from ECETOC3 all of which highlight that 'lung overload' studies in rats are irrelevant for human exposure. As a consequence we do not believe that the findings in these studies put forward by Anses bear any relevance for humans particularly as the adverse outcome pathways are not comparable between rat and human species.

Beyond TiO2, several other pigments and fillers with similar properties to TiO2 (poorly soluble, inert dusts) would also be effected if such studies are deemed relevant for the purposes of harmonised classification and labelling.

2. Observations of inhalation toxicity in humans
Inhalation exposure to TiO2 can be primarily expected in the work place as the majority of TiO2 used in professional or consumer environment would be in the form of a suspension where the particle caused inflammatory effects are not induced. To date many epidemiological studies have been conducted, covering some 24,000 workers, all of which show no evidence of a cancer risk to humans4-8. Furthermore the CLH report itself clearly states that 'human data does not suggest an association between occupational exposure to TiO2 and risk of cancer' (page 8).

3. Occupational exposure to TiO2
The UK COSHH regulations govern the health and safety of worker exposure to chemical substances. Under these, manufacturers are required to undertake risk assessments for their processes and take action accordingly to prevent exposures. Manufacturers of TiO2 comply with these regulations ensuring correct ventilation systems are employed along with the wearing of appropriate PPE.

4. Legal implications
Under REACH, the classification of TiO2 as a carcinogen could trigger either a restriction or subject to the authorisation process. Imposing any one of these REACH processes on TiO2 would have serious knock-on effects on a wide range of consumer products sold in Europe, specifically in the paints, coatings and inks sector where TiO2 is the most widely used pigment currently with no viable alternatives.
Beyond REACH, several other legislative requirements are triggered due to the introduction of a harmonised classification (E.g. Industrial Emissions Directive, Waste Framework Directive, Biocide Product Regulation etc.). More importantly some of these legislations consist of prominent elements of hazard-based decision-making with a number of generic, automatic risk management responses based on CLP outputs. A clear example of this is for biocides where the legislation has clear exclusion criteria which are purely hazard based for certain endpoints such as CMRs. A harmonised classification of TiO2 as a Carc Cat 1B would mean that several relevant consumer products which are not regulated under legislation and currently allowing for a risk assessment for safe use to take place would no longer be available.
Summary
The CIA is of the opinion that the proposed classification put forward by Anses does not reflect an accurate, science based justification to conclude TiO2 as being a carcinogen,

category 1b. The implications on products containing TiO2 in the consumer market would likely be significant, forcing the EU market to rely on poorer performing alternatives which are less cost-effective both from an economic and environmental perspective. CIA is concerned that the unfounded approach being used for TiO2 could also be applied to other substances with similar properties. We therefore ask that all data used in such submissions, in this case lung overload rat data, is scientifically justified, scrutinised and meets with current science consensus before it reaches the final decision stages.

References

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2. http://www.oecd-ilibrary.org/environment/guidance-document-116-on-the-conduct-and-design-of-chronic-toxicity-and-carcinogenicity-studies-supporting-test-guidelines-451-452-and-453_9789264221475-en, page 71, Section 135.
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6. Ellis, E.D. et al. (2010): Mortality among titanium dioxide workers at three DuPont plants, J Occup Environ Med. 52(3), pages 303-9
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8. Fryzek, J.P. et al. (2003): A Cohort Mortality Study Among Titanium Dioxide Manufacturing Workers in the United States, J Occup. Environ. Med 45, pages 400-409

ECHA note – A non confidential attachment was submitted with the comment above. TIO2 proposal_CIAresponse FINAL.pdf

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain	EEIG for Inorganic Pigments	BehalfOfAnOrganisation	69

Comment received

The proposed classification and labeling for titanium dioxide by the French MSCA would have serious and disproportionately negative impacts on the European market regarding the products manufactured by our member companies.
Titanium dioxide is commonly used in the inorganic pigments sector in Europe. Within our industry (SMEs concentrate the major number of European companies), titanium dioxide is one of the most prominent raw materials; indeed, the production of complex inorganic colour pigments and preparations with Ti-content cover quantities up to several thousands Tn/year.
It is used as starting material for the synthesis of important inorganic coloured pigments (e.g. with rutile type structure). Here, titanium dioxide is fully converted during the production process. As a structure-giving component, titanium dioxide is the indispensable basis for the manufacture of these colour pigments.
These complex inorganic pigments are used mainly in ceramic sector and also in other surface applications like plastics, coatings…

Typical concentrations of titanium dioxide in complex inorganic pigments are between 1 and nearly 100%. The TiO2 concentration in final mixture strongly depends on the application. Inorganic Pigments and preparations containing Titanium dioxide are firstly used in industrial applications. ECHA note – A non confidential attachment was submitted with the comment above. 14072016_EEIG. IP inpult CLH Titanium dioxide-final .pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	KRONOS INTERNATIONAL, Inc.	BehalfOfAnOrganisation	70
Comment received				
KRONOS is a manufacturer of titanium dioxide (TiO2) with six production locations, four of which are located in Europe, and two are based in North America. Production started in 1916, and during this century of producing TiO2 – following the respective provisions of industrial hygiene and complying with workplace exposure levels when and where they existed - there was no indication of an increased mortality rate caused by non-malignant respiratory tract diseases or lung cancer among the workers. In the dossier submitted by the French agency ANSES it is pointed out several times that the carcinogenic mode of action is that of biopersistent granular dusts (e.g. pages 8, 58, and 69). Should titanium dioxide as one representative of the biopersistent granular dusts or poorly soluble particulates (PSP) be classified according to the proposal as being a potential human carcinogen, the classification of other representatives of the same class of substances, namely other pigments and fillers of mineral origin, would only be a logical consequence, thereby ultimately depriving whole industries of potential alternatives to TiO2. In many sets of European as well as national legislation – e.g. on cosmetics, on toys, but also on industrial plant safety, and environmental and consumer protection, on waste law – classification and labelling give rise to comprehensive obligations and bans or restrictions, automatically and without any further examination of whether the use of the sub¬stance really poses risks. Therefore, even though the proposed classification is associated to a specific route of exposure – inhalation, the production and marketing of products containing TiO2 above the concentration limit would automatically lead to restrictions to or ban of such products even though the titanium dioxide will be enclosed in a matrix thus rendering the exposure by inhalation irrelevant. Over the last decade there was a paradigm shift regarding inhalation studies performed under lung overload conditions, their interpretation and relevance for humans which can be seen in guidance documents and other publications by academically renowned organisations such as ECHA (ECHA Guidance Document on CLP, chapter 3.9.2.5.3), ECETOC (ECETOC Technical Report 122 "Poorly soluble particles / Lung Overload"), and				

OECD (Guidance document No. 116 on the carrying out of carcinogenicity studies). These organisations came to the overall conclusion that studies under overload conditions should be avoided (OECD) and that findings of such studies should not be used for classification.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom		BehalfOfAnOrganisation	71

Comment received
We fully support and agree with the position of the TDMA/TDIC position of no classification for TiO2. Our majority and critical use of TiO2 is for the manufacture of our intumescent coatings. We also use smaller volumes in sealants and adhesives. Intumescent coatings protect the structure of a building in the event of a fire and therefore provide protection ultimately to people and the preservation of human life. The function of TiO2 in intumescent coatings is as a nucleating agent and a main component of the developed char. It is absolutely critical to product performance. Alternatives to TiO2 in this role have been researched over time, however none have ever been successfully identified. A carcinogenic classification would severely affect and impact our products in terms of; - restriction to products for professional use only, - increased hazard labelling, - no possibility of meeting any Ecolabelling criteria, - increased Risk Management Measures for our production workers, - customer reluctance to purchase TiO2-based products, - global impact (as other countries follow), - hazardous waste classification, - follow-on effects with other insoluble powders. The historical use of TiO2 in our industry has never shown any negative effects to human health to the best of our current knowledge. We are confident of safe use by; - RMM (Risk Management Measures) to protect handling operatives in manufacturing, - complete encapsulation of the material in a liquid product matrix giving no rise to human exposure after application.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Albemarle Europe SPRL	BehalfOfAnOrganisation	72

Comment received

Albemarle Europe SPRL greatly appreciates the opportunity to comment on the Annex XV dossier for harmonized classification of Titanium dioxide, CAS No. 13463-67-7, EC-No. 236-675-5 submitted by France with the proposed classification as carcinogen cat. 1B – H350i.
An accurate hazard classification of a widely used chemical is extremely important. If a chemical's actual hazards are understated, worker safety or public health might be jeopardized via permitting inappropriately high levels of exposure. Less appreciated are the potential adverse consequences of overstating the actual hazards. Widely used industrial chemicals achieved their marketplace acceptance through competitive and dynamic selection and deselection processes. An important factor in industrial chemical selection is the level of hazard to human health and the environment. If the hazard setting process is a sliding scale wherein the evidentiary burden on chemicals evaluated more recently is higher than that experienced by similar chemicals evaluated during an earlier time period, customers might switch to an alternative chemical that might, or might not be, less hazardous in actuality. The proposed classification of titanium dioxide as a possible human pulmonary carcinogen represents just such a case of over-classification that is not supported by the extant scientific evidence.
The particular case of the proposed over-classification of titanium dioxide as a possible human pulmonary carcinogen is problematic for producers, downstream customers and consumers. Much more importantly due to its potential impact on the entire chemical spectrum, is that implementation of the methodology that leads to this over-classification is outside the historical norms of the classification process, and encroaches upon the informational utility of the 'not classifiable' and 'not carcinogenic' categories.

We would like to draw your attention to an excellent review of the toxicological literature related to poorly soluble particles, and includes titanium dioxide, that Peter Morfeld et al. published in 2015 [Peter Morfeld, Joachim Bruch, Len Levy, Yufanyi Ngiewih, Ishrat Chaudhuri, Henry J Muranko, Ross Myerson and Robert J McCunney; Translational toxicology in setting occupational exposure limits for dusts and hazard classification – a critical evaluation of a recent approach to translate dust overload findings from rats to humans; Particle and Fibre Toxicology (2015) 12:3DOI 10.1186/s12989-015-0079-3.] Morfeld et al. (2015) discuss a comprehensive range of relevant topics, but for the purpose of this discussion the following points are relevant:

1) Epidemiology studies on a variety of insoluble particles of low toxicity have not shown an increased risk of lung cancer in occupationally-exposed workers.
2) Rats are a uniquely susceptible species to the adverse effects of insoluble particles under overload conditions including development of lung tumors.
3) For rats to develop lung tumors from particle overload, the inflammation has to be severe enough to cause fibrosis. Thus, lung tumor formation even in rats is a high-dose effect.
4) Robust inflammation-induced rat lung tumors develop through a well-studied sequence of epithelial cell damage, reparative hyperplasia, followed by tumor formation. There is nothing unique at the cellular level regarding the mechanism of rat lung tumor development in insoluble particle overload.
5) Titanium dioxide is not a genotoxin.
6) Primates in controlled exposures to coal dust and/or diesel exhaust do not develop adverse lung changes similar to rats.

7) Coal miners have impaired particle clearance but only develop fibrosis and not cancer as the particles move from alveoli to the interstitium. Some of the conclusions reached by Morfeld et al. (2015) include: "1) GBS cause lung cancer in rats due to chronic inflammation as a result of dust overload in the alveolar region of the lung. 2) If clearance mechanisms are not overwhelmed and, thus, inflammation is prevented, lung cancer risk will not be increased. Since excess lung cancers in the rat are only observed in conditions of lung overload, a threshold exists for adverse effects from exposure to these types of dusts. 3) Classifying all GBS as carcinogenic to humans based on rat inhalation studies in which lung overload leads to chronic inflammation and cancer is inappropriate. Studies of workers, who have been exposed to relevant levels of dust, have not indicated an increase in lung cancer risk."
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Portugal	Portuguese Paint Association	BehalfOfAnOrganisation	73
Comment received				
The Portuguese Paint Association (APT) represents 85% of the Portuguese paint industry, which is worth approximately 500 million euros split between architectural coatings (58%), industrial coatings (35%), vehicle refinish coatings, protective coatings and marine coatings. This industry employs more than 4 000 people in Portugal and has a Gross Value Added of 230 million euros. According to this relevance, we are concerned about the proposal made by ANSES to change titanium dioxide (TiO2) classification to a category 1B carcinogen, since it would bring serious negative impact on the European and Portuguese paint and coatings market. This substance is widely used (about 20% of total raw materials) in this sector, being a key material to the manufacture of paint products. The proposed classification would affect not only the chemical mixture of the paint, since there are no alternative substances with the same quality and performance as titanium dioxide, but also our market and consequently our members, as products containing this substances would no longer be permitted for sale to the general public, putting actually an end on the DIY market. This would also mean that there would need to be special safety measures for professional and industrial users demanding extra costs on an already burdened industry. Based on studies from reputable organizations having shown that TiO2 is safe to use and given the negative consequences of this proposed classification and labelling, we believe that this proposal should be declined.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	VOCO GmbH	BehalfOfAnOrganisation	74

Comment received

The argumentation of the CLH report to classify TiO2 as Carc. Cat 1 B – H350i is scientifically not substantiated.

Reasons:
1.) The statement that there is sufficient evidence in experimental animals for the carcinogenicity of titanium dioxide (underlining not added, CLH report, page 8, 4th paragraph) is taken from an IARC monograph. The statement was published in the 2006 IARC edition on TiO2 as well as in the 2010 edition. However, the statement is incompletely quoted. In fact, the sentence prior to the above statement reads "There is inadequate evidence in humans for the carcinogenity of TiO2." (please see the 2010 edition, page 275, paragraph 6.2/ underlining added).
Scientifically it is completely unjustifiable to take one assessment but to be silent on the other, by far more important, assessment.

2.) The proposed classification "Cat.1" means that it is known or presumed that TiO2 has carcinogenic potential for humans. This conclusion however directly contradicts the finding of IARC ("inadequate evidence").

3.) The German Federal Institute for Risk Assessment (BfR) and the German Federal Environmental Agency (UBA) both published a common assessment with the titel "Beurteilung eines möglichen Krebsrisikos von Nanomaterialien und von aus Produkten freigesetzten Nanopartikeln" (assessment No 005/2011). In this paper special attention was drawn to TiO2 (please see pages 4 to 10). On page 7, last paragraph, this assessment concludes "Zur karzinogenen Wirkung von Nano-TiO2 kann gegenwärtig keine endgültige Aussage für den Menschen getroffen werden. Auf der Basis der Tierdaten ist lediglich ein Verdacht auf ein karzinogenes Potential von Nano-TiO2 für den Menschen auszusprechen, da die bisher vorliegenden Untersuchungen diesbezüglich nicht hinreichend belastbar sind."

4.) The conclusion of the BfR and UBA is in line with the finding of IARC as well as with the assessments of the US agencies NIOSH, NTP, OSHA and EPA.

5.) Based on the observations above, it is requested to reject the proposal submitted by the CLH report.

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

Specific responses to

1) and 2) The complete IARC conclusion is that TiO2 "is possible carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies". This is considered consistent with proposed classification Carc 1B "presumed carcinogen".
4) References are lacking to be adequately taken into account.

RAC's response

Noted. The opinion compares the conclusions of the IARC assessment with the RAC proposal.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Japan	Japan Chemical Industry Association	BehalfOfAnOrganisation	75

Comment received

Currently there is no globally unified clear classification of Carcinogenic effect on TiO2. While we understand that the IARC evaluated TiO2 as 2B in its carcinogenic effect which is one of the most sever classification, French proposal of "1B" is not scientifically well understandable since it is based on the same information utilized by the IARC.
We sincerely appreciate an appropriate categorization and regulation considering human health and environment, on the other hand, we are really anxious about the categorization which raise unnecessary concern and too much regulation against proper development industrial culture.

ECHA note – A non confidential attachment was submitted with the comment above. TiO2_CLH_20160715_JCIA_EN Final.pdf

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM.

Specific response to point (1) of the attachment, some "classifications" of TiO_2 by international organizations are lacking such as classification by the MAK Commission (category 4 carcinogen known to act typically by non- genotoxic mechanisms) and by OEHHA (carcinogen under proposition 65).

RAC's response

Noted. The opinion compares the conclusions of the IARC assessment with the RAC proposal.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Keramische Industrie eV	BehalfOfAnOrganisation	76

Comment received

BVKI, the confederation of the associations of the German Fine Ceramic Industry, covers a wide range of products including sanitary ware, table & decorative ware, technical ceramics and abrasives.
In addition to its wide spread use as a white pigment in glazes, Titanium dioxide is also present, up to 4%, in a number of naturally occurring minerals that are used in the ceramic industry. TiO2 is also an essential raw material for the production of different types of technical ceramics and abrasive products.
As a result, the proposed classification of TiO2 would impact the classification of raw materials and body preparations with consequences on all other European or national regulations which are based on the CLH classification of a material.
The CLH dossier proposes the same classification for all forms of TiO2. This goes against the scientific conclusions drawn by Wang and Fan in 2014 (International Journal of Molecular Science, 2014, 15, 22258-22278; doi:10.3390/ijms151222258; article entitled: Lung Injury Induced by TiO2 Nanoparticles Depends on Their Structural Features: Size, Shape, Crystal Phases, and Surface Coating).
No cases of pulmonary fibrosis were observed among TiO2-exposed employees. The study of Dupont "Epidemiologic study of workers exposed to titanium dioxide." J Occup Med. 1988 Dec;30(12):937-42 gave the same result.

We believe that there is not enough scientific evidence in the dossier as presented by France for a harmonised classification of TiO2 as a carcinogen cat. 1B. BVKI fully supports the general and specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA), the Titaniun Dioxide Industry Consortium (TDIC) and the Industrial Minerals Association (IMA-Europe) as well as the comments submitted by Cerame-Unie.
Dossier Submitter's Response
See points 1, 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	German Refractory Association	BehalfOfAnOrganisation	77
Comment received				
The production capacity/output of the members of the German Refractory Association (VDFFI) represents about 70% of the total amount of refractory products manufactured in Germany and about 25% of the European refractory production. The proposal to classify TiO2 as Carc. 1B is based on pulmonary inflammation due to the biopersistence and poor solubility of TiO2 in connection with an overload effect. This effect is not a substance-specific one and relates to almost all poor soluble substances. Since an inhalative exposure of TiO2 dust is almost exclusively to be expected in the workplace, the exposure level should be regulated by directives on occupational safety and health (OSH). The classification of TiO2 as Carc. 1B would not improve the level of protection, but would cause a large negative socio-economic impact and significant administrative cost without better worker protection. Following the idea of "better regulation" under the REFIT agenda, any regulating measure should achieve the most effective level of protection together with minimum (administrative) cost and minimised unfavourable consequences. Most of the raw materials used in the refractory industry, e.g. clays, kaolins, bentonites, bauxites, .., contain TiO2 in form of the crystal phases of rutile and anatase at a concentration up to 4%. A classification of TiO2 as Carc. 1B would - according to the CLP-Regulation- require a classification of these natural materials and refractory products as Carc. 1B and would also render these raw materials and our products to dangerous waste. Conclusion The classification of TiO2 as Carc. 1B is not the proper answer for better worker protection, as the same level of protection can be achieved by using more targeted directives on occupational safety and health (OSH) and effective and appropriate risk management measures for worker protection with less administrative costs, much less negative socio-economic consequences.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Carbon Black For REACH Consortium	BehalfOfAnOrganisation	78

Comment received

Response to the ANSES report on Titanium Dioxide by the Carbon Black for REACH Consortium

Executive Summary:

The Carbon Black for REACH Consortium (CB4REACH) offers comments on the CLH report, submitted by ANSES and proposing a harmonised classification and labelling for Titanium Dioxide (TiO2) for the carcinogenicity endpoint (ECHA 2016). Scientific and medical experts of the Scientific Advisory Group (SAG) of the International Carbon Black Association (ICBA) developed these comments on behalf of the CB4REACH Consortium. As members of ICBA's SAG, we have overseen and conducted numerous peer-reviewed epidemiology, toxicology and industrial hygiene studies related to carbon black (CB), a substance often described - like TiO2 - as a poorly soluble particle (PSP).

We offer these comments as many of the scientific issues raised in the ANSES CLH report are based, not only on TiO2, but on other respirable PSPs, including CB, a substance, which has been extensively investigated, through CB-exposed production worker studies for mortality and morbidity effects as well as through many informative rodent inhalation studies and in vitro investigations.

We have specifically commented on three key aspects, namely:

(1) ANSES's evaluation of the significance to humans of lung overload endpoints in laboratory rodents; and in particular lung cancer in the rat; and

(2) An evaluation of the epidemiology literature of coal miners as it relates to lung overload in rats. In general, ANSES concludes that rat inhalation studies in which lung overload is associated with cancer should be used in human risk assessment, most notably for risk of lung cancer. The ANSES CLH report, however, ignores the vast literature of mortality studies of TiO2, coal miners and CB production workers, in which lung cancer risk was not elevated, even among the most heavily exposed coal miners who developed Coal Workers pneumoconiosis (CWP) or in the TiO2 and CB production workers.

(3) The overall evidence base does not meet the CLP criteria for classification for carcinogenicity of Carc. Cat 1B – H350i as proposed in the ANSES CLH report.

Although there is clear evidence that PSPs can cause lung cancer in rats under conditions of particle overload, the evidence from other rodent species (such as mice and hamsters) and a wealth of relevant and well-conducted epidemiological investigations, not addressed in the ANSES report, strongly supports the contention that the lung tumour response, seen in rats, is unique to that species under overload conditions and related to an exaggerated inflammatory response causing a secondary (non-direct genotoxic) carcinogenic mode of action (Morfeld et al., 2015; ECETOC, 2013).

Our considered view is that if one used a weight of evidence approach, as recommended by ECHA in its Guidance on information requirements and chemical safety assessment - Chapter R.4: Evaluation of available information, and envisioned by the CLP regulation (section 1.1.1 of Regulation (EC) No 1272/2008), and included epidemiological studies,

experimental interspecies differences and mode of action findings, and accepted that lung tumours induced by PSPs such as TiO2, were unique to the rat and not predictive for humans, then no classification would seem far more appropriate and consistent with the science base. ECHA note – A non confidential attachment was submitted with the comment above. ANSES Proposed Classification of TiO2 - Comments by CB4REACH - 14 July 2016 - FINAL.pdf
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Carbon Black For REACH Consortium	BehalfOfAnOrganisation	79
Comment received				
Response to the ANSES report on Titanium Dioxide by the Carbon Black for REACH Consortium Executive Summary: The Carbon Black for REACH Consortium (CB4REACH) offers comments on the CLH report, submitted by ANSES and proposing a harmonised classification and labelling for Titanium Dioxide (TiO2) for the carcinogenicity endpoint (ECHA 2016). Scientific and medical experts of the Scientific Advisory Group (SAG) of the International Carbon Black Association (ICBA) developed these comments on behalf of the CB4REACH Consortium. As members of ICBA's SAG, we have overseen and conducted numerous peer-reviewed epidemiology, toxicology and industrial hygiene studies related to carbon black (CB), a substance often described - like TiO2 - as a poorly soluble particle (PSP). We offer these comments as many of the scientific issues raised in the ANSES CLH report are based, not only on TiO2, but on other respirable PSPs, including CB, a substance, which has been extensively investigated, through CB-exposed production worker studies for mortality and morbidity effects as well as through many informative rodent inhalation studies and in vitro investigations. We have specifically commented on three key aspects, namely: (1) ANSES's evaluation of the significance to humans of lung overload endpoints in laboratory rodents; and in particular lung cancer in the rat; and (2) An evaluation of the epidemiology literature of coal miners as it relates to lung overload in rats. In general, ANSES concludes that rat inhalation studies in which lung overload is associated with cancer should be used in human risk assessment, most notably for risk of lung cancer. The ANSES CLH report, however, ignores the vast literature of mortality studies of TiO2, coal miners and CB production workers, in which lung cancer risk was not elevated, even among the most heavily exposed coal miners who developed Coal Workers pneumoconiosis (CWP) or in the TiO2 and CB production workers. (3) The overall evidence base does not meet the CLP criteria for classification for				

carcinogenicity of Carc. Cat 1B – H350i as proposed in the ANSES CLH report.

Although there is clear evidence that PSPs can cause lung cancer in rats under conditions of particle overload, the evidence from other rodent species (such as mice and hamsters) and a wealth of relevant and well-conducted epidemiological investigations, not addressed in the ANSES report, strongly supports the contention that the lung tumour response, seen in rats, is unique to that species under overload conditions and related to an exaggerated inflammatory response causing a secondary (non-direct genotoxic) carcinogenic mode of action (Morfeld et al., 2015; ECETOC, 2013).

Our considered view is that if one used a weight of evidence approach, as recommended by ECHA in its Guidance on information requirements and chemical safety assessment - Chapter R.4: Evaluation of available information, and envisioned by the CLP regulation (section 1.1.1 of Regulation (EC) No 1272/2008), and included epidemiological studies, experimental interspecies differences and mode of action findings, and accepted that lung tumours induced by PSPs such as TiO2, were unique to the rat and not predictive for humans, then no classification would seem far more appropriate and consistent with the science base.

ECHA note – A non confidential attachment was submitted with the comment above. ANSES Proposed Classification of TiO2 - Comments by CB4REACH - 14 July 2016 - FINAL.pdf

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece	N. KRALLIS S.A.	BehalfOfAnOrganisation	80

Comment received

I represent the company N KRALLIS SA established in Greece and respond on behalf of that company. We are an agent-distributor of Titanium Dioxide and are concerned about the proposal made by France for classifying it as a carcinogen. Our company currently employs 45 people. We have been working with this substance for 57 years. As we successfully manage the workplace exposures of dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.
TiO2 is a key material for our business and the products of all of our clients. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public) and to our company.

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Czech Republic		Individual	81

Comment received

I am not toxicologist; however, this proposal seems to me rather misguided.
All studies in which the result is that TiO2 does not cause any effect are dismissed

including quite huge epidemiological studies. On the other hand, studies which resulted in some effects are accepted regardless of their problematic issues.
As I said, I am not toxicologist so I can only comment some obvious facts. In NCI, 1979 study animals are fed up to 7500mg/kg bw/day. If you recalculate it to 80kg human he/she should eat each day 600 g of inert material, what seems ridiculous to me. The same can be said about some inhalation studies (Lee 1985, 1986) where dust concentration of 250mg/m3 can be seen only in volcanic eruptions, sandstorms or industrial explosions. I calculated that visibility in such conditions is around 20 m (based on Baddock, M.C. et al, 2014. A visibility and total suspended dust relationship. Atmospheric Environment, 89, pp. 329 – 336). However more precise calculation based on Mie theory and particle size of pigmentary TiO2 lead to visibility of only around 6 m (William C. Hinds, Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles, 2nd Edition February 1999, ISBN: 978-0-471-19410-1). It means, that in such concentration one cannot see a black object on white background unless it is closer than 6 m. Evaluating chronic influence in such environment is torturing of animals. Nobody is able to work in such environment for longer time period.
Other important study seems to be Pott and Roller (2005) If I understand correctly, they found that most GBP led to tumour formation and TiO2 is specifically mentioned (page 31-32). Interestingly in re-evaluation (Becker 2011) was found that 30 mg instilled TiO2 resulted in 50% animals with tumour but 60 mg instilled TiO2 resulted only in 21% of animals with tumour. From layman point of view, it means negative dose response effect.
If you accept the CLH proposal based on some not very reliable findings and more or less research studies and do not take into consideration negative outcome of epidemiological findings you do bad service both to general public and toxicological community. Intrinsically safe material (TiO2) will be included in the same category as e.g. chromates or benzo[a]pyrene. It can result in lowering awareness to real hazards in general public. And for toxicological community it means, that even studies which clearly exceed any reasonable exposition level can be performed and accepted as relevant to the risk evaluation.

Dossier Submitter's Response

See point 2 and 4 of the attachment to the RCOM.

Specific reponse on the statement: "*Interestingly in re-evaluation (Becker 2011) was found that 30 mg instilled TiO2 resulted in 50% animals with tumour but 60 mg instilled TiO2 resulted only in 21% of animals with tumour*". Please note that it is not the same form of TiO2 that resulted in 50% or 21% animals with tumour as detailed in page 32 of the CLH report: "*A re-evaluation of the histopathological findings of this study established that 30 mg of instilled nano-TiO2 induced tumours in 50% of the animals studied, whereas after instillation of a total of 60 mg of fine TiO2, tumours were found in 21% of the animals studied.*"

RAC's response

Noted. The RAC proposal for classification of TiO2 is mainly based on inhalation studies.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Italy	Huber Italia SpA	BehalfOfAnOrganisation	82

Comment received

I represent the company Huber Italia SpA, which operates in Italy as an European member of hubergroup, and respond on behalf of that company. We are a formulator of printing inks and related products and are very concerned about the proposal made by France for classifying titanium dioxide as a carcinogen.
Our company currently employs about 120 people. TiO2 is a key material to manufacture

our products, being used in about 40% of our production. We understand that the consequence of the proposed classification would negatively affect our production and our markets. To date, no alternative material with comparable properties (opacity, whiteness, …) is available on the market. Without Titanium Dioxide White printing inks will not be available in the same quality anymore. This might even have an influence on quality and safety of food packaging, as the white printing ink layer is not only used for decorative reasons but also e.g. for protection against degradation by light. With regard to the toxicological assessment, we therefore strongly believe that the proposal is disproportionate to the risks posed to human health and would have serious negative impacts to our company as well as to the economy. ECHA note – A non confidential attachment was submitted with the comment above. Statement-HuberItalia-TitaniumDioxide.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	P.A. Jansen GmbH u. Co., KG	BehalfOfAnOrganisation	83
Comment received				
I represent the company P.A. Jansen GmbH u. Co.,KG established in Bad Neuenahr-Ahrweiler, Germany and respond on behalf of that company. We are a formulator of special painter products and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 75 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	ECKART GmbH	BehalfOfAnOrganisation	84
Comment received				
Titanium dioxide has been widely used for many years in industrial as well as in consumer applications. For this reason extensive experiences as well as data in the practical handling of titanium dioxide are available. According to our information none of the available data suggest an association between occupational exposure to titanium dioxide and risk for cancer. Titanium dioxide is used deliberately in cosmetics and plastics applications due to the achromatic bulk color, inert chemical structure and due to the very high purity level with regards to heavy metal traces. Titanium dioxide as a component of pearlescent pigments is widely used for optical applications (e.g. cosmetics, plastics, paints & coatings) and also in functional applications (e.g. sunscreen, IR-reflective materials and paints).				

If titanium dioxide was banned / significantly restricted for cosmetic use (CMR substances are not allowed for use in cosmetics in Europe), the most important colorant (and UV screening agent) for cosmetic and personal care applications would be lost: Titanium dioxide as a component of pearlescent pigments is widely used in the cosmetic sector as an ingredient in color cosmetics, skin care, oral care and personal care products. Similarly, titanium dioxide is the most important white pigment in plastics, paints and coatings. Also pearlescent pigments which contain titanium dioxide are widely used as colorants. In addition to the decorative effects those pigments are also placed in technical applications (Energy Management, Solar und IR-Reflection material, greenhouse applications) utilizing the physical-chemical properties of titanium dioxide pigments / titanium dioxide containing pigments Lacking an appropriate replacement, the consumer market would be heavily impacted by the loss of such a key ingredient.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Netherlands	Baril Coatings B.V.	BehalfOfAnOrganisation	85
Comment received				
Dear ECHA representatives, We are responding to your call to open the public consultation on the French Dossier to classify TiO2 as carcinogenic. I represent the company Baril Coatings B.V. established in the EU Member State the Netherlands and respond on behalf of this company. We are a formulator of paint, lacquers and colorants and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs approximately > 200 people in the EU (and in total > 250 people worldwide). We have been using this substance for more than 25 years. As we successfully manage the workplace exposures of dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public) and to our company. Sincerely, <confidential>				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Japan	Kao Corporation	BehalfOfAnOrganisation	86
Comment received				
IARC which is an intergovernmental agency forming part of the World Health Organization of the United Nations classify TiO2 as 2B. We consider that the proposal from France, "classifying TiO2 as 1B on carcinogenicity" is excessively conservative notwithstanding it is evaluated by the same data as other organizations including IARC. TiO2 is utilized in many industries and it even contributes to our health. For instance TiO2 is very effective UV filter in sunscreen products that protects our skin from severe damage from sunlight. Although we respect the position that suspicious levels of a substance should be restricted, we do not accept a proposal that overestimates a risk and disturbs growth of the industry. We suggest ECHA and RAC to make an appropriate decision based on the sound science.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	New Zealand	New Zealand Paint Manufacturers Association	BehalfOfAnOrganisation	87
Comment received				
ECHA note - Only a non confidential attachment was submitted. ECHA Proposed Classification of TiO2.pdf				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	American Cleaning Institute	BehalfOfAnOrganisation	88
Comment received				
A large body of data demonstrates that TiO2 does not present a cancer risk for humans and the toxicological data do not support the proposed CARC 1B-H360i entry for TiO2 in Annex VI of the CLP Regulation. We refer to the detailed review provided by the Titanium Dioxide Manufacturers Association (TDMA) and the Titanium Dioxide Industry Consortium (TDIC) under this consultation, which ACI supports. Specifically, TDMA and TDIC's submission includes the following evidence that TiO2 does not warrant classification as a carcinogen: • Epidemiological studies of workers have shown no increase in lung cancer and no evidence indicating a "causal relationship" between exposure to TiO2 and development of lung cancer in humans • The observed effects in rats at the exposure levels overloading the lungs are not applicable to humans due to different adverse outcome pathways. Positive animal data from inhalation exposure are only observed in one species at an exposure exceeding the Maximum Tolerated Dose (MTD). The high dosing levels produced conditions of lung				

overload that led to overwhelming of lung clearance mechanisms, resulting in oxidative stress, chronic inflammation and tumor formation. Such testing levels are inconsistent with OECD guidelines 451/116, which recommend that the maximum dose be selected not to "overwhelm normal pulmonary clearance mechanisms". Furthermore, similar effects were not observed in non-rat rodents such as mice, hamsters and rabbits. Extrapolating to humans based on a species-specific toxicological effect that occurs at very high doses exceeding the MTD is not warranted.
• Consistent with the carcinogenicity studies, genotoxicity studies demonstrate that TiO2 is not a primary genotoxicant and only under lung overload conditions is there secondary genotoxicity via the induced inflammation and the associated oxidant generation from inflammatory cells. This is considered to be a threshold mechanism of action that would not occur at lower doses of exposure.

Available data in animals and humans indicate that the carcinogenicity observed in rats under conditions where the lungs are overloaded is not relevant to humans. As such, TiO2 should not be classified as a presumed (Cat 1) nor suspected (Cat 2) carcinogen according to CLP criteria:

CLP annex 1 (3.6.1.1) : "substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans".

In addition, the low level use of TiO2 in detergents, soaps and other cleaning products leads to TiO2 inhalation exposures that are very low.

In summary, ACI supports the submission of TDMA and TDIC, and urges ECHA to not adopt the proposed CARC 1B-H360i entry for TiO2 in Annex VI of the CLP Regulation.

Dossier Submitter's Response

See point 4 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	SPI: The Plastics Industry Trade Association	BehalfOfAnOrganisation	89

Comment received

July 14, 2016

General Comments on the Proposal for Harmonised Classification and Labelling of Titanium Dioxide, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 (1)

The Society of the Plastics Industry, Inc. (SPI) appreciates the opportunity to participate in the Public Consultation for the harmonised classification and labelling (CLH) of titanium dioxide (TiO2) as a carcinogen 1B by inhalation exposure (H350i).

SPI represents the third largest manufacturing industry in the United States. SPI members represent the entire supply chain, including compounders and other users of TiO2 in plastics packaging and other important applications.

Extensive Industry Experience Demonstrates That the Proposed Classification Is Unwarranted

Section 2.2 of the dossier (Identified Uses) recognizes important properties of TiO2, its wide use in industrial settings, and inclusion in numerous products and articles including plastics.

Members within our industry group have extensive experience, over many years, in handling TiO2 as a powder form raw material of various particle sizes. This collective experience and use of TiO2 covers many different industrial operations.

More specifically, primary uses of TiO2 by our members include as an ingredient in polymeric color concentrates, which may be provided in pelletized masterbatch form, and as an ingredient in printing inks applied to foodservice packaging surfaces. End markets include automotive and packaging for food, drug, and cosmetic products. In the vast majority of uses, TiO2 is bound in a polymeric matrix, and controls may be used to prevent inhalation exposures from in-plant material conveyance and scrap regrinding.

It is because of certain functionalities and technical advantages – such as colouring, light protection, UV resistance, thermal stability, good processability, good availability, and compliance with regulations governing food, pharmaceutical, and cosmetic applications including in the EU – that TiO2 is in widespread use by plastic converters, to the extent that TiO2 may be used in almost every color masterbatch formulation a company may make. (2) More than half the composition of a colorant may be TiO2; for example, one company manufactures plastic parts with colorant containing up to 60% TiO2, with the colorant being used around 2% in those particular parts.

Through all of this workplace activity, based on the information we have collected, our members have not seen, nor are they aware of any instance where TiO2 has been associated with causing any form of cancer.

The extensive use and experience should be taken as further evidentiary information that classification of TiO2 as a human carcinogen by inhalation is not warranted.

Available Epidemiological Data Requires Greater Consideration

We appreciate acknowledgement in the report (page 8) that "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer."

Given a statement in the report (page 49) that epidemiological data were considered inadequate, in the context of methodological limitations and absent certain data regarding particle size and distribution, additional data should be examined. A more complete assessment would include the study by Ellis et al (2010, 2013 – conducted after the IARC classification), in which there was no evidence of lung cancer associated with TiO2 exposure. (3) In addition, the lack of an exposure effect is supported by two Canadian case-control studies (e.g., Boffetta et al 2001) which included over 2000 cases of lung cancer. (4) Indeed, the Canadian Centre for Occupational Health & Safety recognizes that: "However, it should be noted that the human studies conducted so far do not suggest an association between occupational exposure to titanium dioxide and an increased risk for cancer" (https://www.ccohs.ca/headlines/text186.html).

While epidemiological studies do not necessarily negate well-conducted animal studies, as provided in Annex I, section 1.1.1.4 of the CLP Regulation, the inadequate consideration of strong epidemiological evidence is inconsistent with the regulation. The same section of

the Annex acknowledges potential limitations but also includes: "Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data."

The Proposal is Not Supported by New Evidence

We observed that numerous studies cited in the report were published after IARC's 2006 classification, yet of the four studies included in Table 4.1-01 (Summary table of relevant carcinogenicity studies) for relevance for the inhalation route (for which this classification is being proposed), none were published after 2006. As the IARC classification is disputed, and the proposal does not rely on any inhalation study since then, the case for classification is not sufficiently supported.

Discrepancies in the Report Should Also Put Aside the Proposed Classification

Just as too many CLH discrepancies with existing data led to the initial proposal for a harmonized classification for mutagenicity to be put aside (report pages 7-8), with the number of discrepancies remaining in the report, the proposal for carcinogenicity by the inhalation route should also be abandoned. We offer the following examples.

Page 4: "…the main proposed mechanism of carcinogenicity by inhalation is thus based on the low solubility and biopersistency of the particles leading to pulmonary inflammation then oxidative stress. Secondary genotoxicity and cell proliferation result in carcinogenicity. Nevertheless, possible direct genotoxicity cannot be excluded." With such confidence in this secondary mechanism, and lack of evidence for direct genotoxicity, the last statement is overreaching and should not be included absent adequate supporting data.

Page 49: "In the first study (Lee, 1985)… Squamous cell lesions, classified as cystic keratinizing squamous cell carcinoma by the authors, were found in 1 male and 13 females at the same exposure concentration. A re-evaluation of the proliferative squamous lesions found in this study showed that over the 13 reported in females, only one was confirmed as squamous cell carcinoma (Warheit and Frame, 2006)." Re-evaluation challenged the original findings of the study that received the highest reliability rating for studies relevant to the inhalation route.

Pages 49-50: "Supportive information can be obtained from intra-tracheal studies… Although instillation is not a physiological route for human exposure and even if differences in terms of dose rate, particle distribution or clearance were noted compared to inhalation, similar types of lung tumours… were observed after instillations of TiO2… in female rats (Pott, 2005)… Xu (2010) also reported a carcinogenic promotor potential of nano-TiO2… However, the results from Xu (2010) study need to be taken with caution considering the little experience with this model. In contrast, no promotor potential was reported in the Yokohira et al. publication (2009). However, this study is not judged reliable…" It is unclear how any of this information could be considered supportive, let alone for a physiological route that is not relevant for human exposure.

Page 50: "In conclusion, although no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data, lung tumours were reported in one inhalation study and one intra-tracheal study of acceptable quality. Carcinogenic potential was also reported in two further (inhalation or intra-tracheal) studies of lower reliability but of adequate relevance." However, page 9 notes: "Therefore, classification as Carc. Cat 1B – H350i is justified for TiO2 considering the

increase of both malignant and benign lung tumours in one species, reported in two studies by inhalation and two studies by instillation after exposure to TiO2." This summary statement suggests greater confidence – two studies each – than the more detailed discussion in the report, which better reflects the reliability of one each. This borders on reliance on a single study by the relevant inhalation route, with the appropriateness of a single-study approach under question.

IARC Guidance Recognizes the Single Study Criteria for Classification is Not the Final Word

In 2006, IARC changed their criteria for classification of carcinogens, such that "sufficient evidence of carcinogenicity" can be demonstrated by a single study. One such criterion is: "An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence."
Another criterion is: "A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites." (5)

However, IARC earlier states: "It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity" (http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php). SPI would encourage the Committee for Risk Assessment (RAC) to conduct its own evaluation instead of simply accepting the IARC classification, particularly as IARC failed to follow its own process and overlooked overwhelming epidemiological evidence that TiO2 is not carcinogenic to humans.

Relevancy of Data and Consistency with Guidance

We share concerns with the proposal as raised by the Titanium Dioxide Manufacturing Association (TDMA) and Titanium Dioxide Industry Consortium (TDIC), specifically regarding:

Relevancy of lung overload – such that weight of evidence analysis may result in the discounting of carcinogenic evidence, and species-specific mechanisms reasonably certain to be not relevant for human health shall not justify classification (per the United Nations Globally Harmonized System of Classification and Labeling of Chemicals, and the CLP Regulation, respectively).

Mechanism of action – such that the proposal does not rule out a primary genotoxic mechanism, while at the same time appears to accept the prevailing scientific view that a secondary genotoxic mechanism (from induced inflammation) was responsible for tumours observed in rats. Absent sufficient justification, the relevance for humans should not be conservatively overstated in concluding statements given the scientific evidence for the secondary mechanism.

Insufficient questioning of the relevance of the excessive high-dose induced rat tumours for direct human extrapolation – given that there is no epidemiological evidence of lung cancer induced by poorly soluble particles of low toxicity (PSP) in TiO2-exposed workers, or even in clearly particle-overloaded lungs.

Compliance with relevant ECHA guidance – specifically, regarding adequacy of the Lee et

al. (1985) study for classification purposes, in that the adverse findings were obtained at doses exceeding the maximum tolerated dose. OECD Guideline 451 explicitly states that "inhalation of doses that overwhelm pulmonary clearance may lead to tissue responses that are specific to the species being tested" (section 94, p.54; emphasis added), and notes that robustness of a study depends in part on dose levels that do not overwhelm metabolic/homeostatic mechanisms (which may produce false positive results), and provides further guidance on study design to address potential accumulation in the lungs of poorly soluble substances. Regarding the relevance for humans, ECHA's guidance covers tumors observed at excessive doses and/or only at sites of contact, or only at excessive doses and severe toxicity. (6)

Further Relevance to the Plastics Industry if the Proposed Classification Were to Proceed

We understand that this Public Consultation is focused on the question of classification, and issues related to the impact of a classification have in the past simply received an acknowledgement that they relate to further action (e.g., SVHC or restrictions). Classification and labeling is one outcome if this proposal were to proceed; if TiO2 could not be used, significant challenges would undoubtedly arise.

There is a lack of alternatives that provide comparable technical performance, availability, and regulatory compliance, and therefore there will be significant economic costs for manufacturers to continue making products necessary for daily life. For example, there could be disruptions in the supply and cost of food and pharmaceutical products in light of the widespread currently approved uses of TiO2 as an additive to food and drugs and their packaging in the EU and U.S.

Conclusion

In summary, we believe the proposed classification is not justified, given:

1. The reliance on studies where test animals experienced lung overload, resulting in a response typical of the methodology but of questionable relevancy for human health;

2. Epidemiological data provides evidence of no carcinogenicity, but was insufficiently weighted;

3. Additional relevant epidemiological data was not considered; and

4. TiO2 has been extensively evaluated and remains approved for use in such sensitive applications as food, drugs, and cosmetics, as well as packaging for these products, in various jurisdictions, supporting the case that downstream users are not at risk.

We also support the positions of the TDMA and TDIC – no labelling of TiO2.

We appreciate your consideration of this submission to the Public Consultation. Given the potential consequences of the proposed classification for the plastics industry, we look forward to publication of the opinion of the RAC.

Endnotes

1 Submitted electronically at: https://comments.echa.europa.eu/comments_cms/AnnexXVCLH.aspx?SubstanceName=Titanium%20dioxide&EcNumber=236-675-5%20&CasNumber=13463-67-7

2 In the European Union, TiO2 is cleared for use as a food additive (E171), as a pharmaceutical additive (European Pharmacopeia), as a cosmetic additive (Annex IV of Regulation (EC) 1223/2009), and as an additive or polymer production aid in plastic food-contact materials (Annex I of Commission Regulation (EU) No. 10/2011). In the United States, TiO2 is cleared for use as a direct food additive in accordance with the specifications set forth by the U.S. Food and Drug Administration in the U.S. Code of Federal Regulations (21 C.F.R. Section 73.575). TiO2 is further cleared in the U.S. for use in ingested and externally applied pharmaceuticals at 21 CFR Section 73.1575 and for use in cosmetics at 21 CFR 73.2575. On the basis of these clearances, TiO2 may also be used legally in food-contact applications and in cosmetic and pharmaceutical packaging in the U.S. 3 Ellis ED, Watkins J, Tankersley W, Phillips J, Girardi D. 2010. Mortality among Titanium Dioxide Workers at Three DuPont Plants. Journal of Occupational & Environmental Medicine. 52(3):303-309. 4 Boffetta P, Gaborieau V, Nadon L, Parent ME, Weiderpass E, Siemiatycki. 2001. Exposure to Titanium Dioxide and Risk of Lung Cancer in a Population-Based Study from Montreal. Scandinavian Journal of Work, Environment & Health. 27(4):227-232. 5 World Health Organization. International Agency for Research on Cancer. 2006. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Preamble. 6 ECHA. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1, June 2015. These comments are also being submitted as an attachment to ensure the entire content is received. ECHA note – A non confidential attachment was submitted with the comment above. SPI Comments on Proposed CLH for TiO2 Under the CLP Regulation.pdf
Dossier Submitter's Response
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Mexico	ANAFAPYT	BehalfOfAnOrganisation	90
Comment received				
We believe that the consequences of the proposed classification would clearly be disproportionate to any speculative risks posed to human health, and we urge that it be rejected. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - ECHA - ANAFAPYT_july_2016.pdf				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	Aerospace Industries Association	BehalfOfAnOrganisation	91
Comment received				
The Aerospace Industries Association (AIA) appreciates the opportunity to make comment on the proposal regarding harmonised classification and labelling of substances on Titanium dioxide. AIA represents over 330 major U.S. aerospace and defense manufacturers and suppliers of civil, military, and business aircraft, helicopters, unmanned aerial systems, missiles, space systems, aircraft engines, material, and related components, equipment services, and information technology. The aerospace industry is inherently global, and many of our major suppliers are located in the European Union. Titanium dioxide is a critical substance used in broad range of applications in the aerospace industry. For example, as a widely used pigment titanium dioxide provides whiteness, opacity, thermal stability, reflection, and UV blocking capability in topcoats, primers, specialty coatings, adhesives, and leveling compounds. It also acts as a heat stabilizer providing necessary dry heat resistance in products such as silicone rubbers. Furthermore, aerospace products must meet stringent requirements that are essential to the safety and reliability of our products. These requirements drastically increase the technical risk involved with developing, qualifying, certifying and implementing alternative materials and processes.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		Individual	92
Comment received				
The different sizes of TiO2 needs to be differentiated in toxicological evaluations, which is missing in the CLP report. Therefore a complete revision is needed - and studies needs to be more critically reviewed. ECHA note – A non confidential attachment was submitted with the comment above. ECHA_ CLP_Comment.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Advanced Chemical Specialties Ltd	BehalfOfAnOrganisation	93
Comment received				
The re-classification of all forms of titanium dioxide is based on evidence obtained in lung congestion tests on one species of rat, which has a propensity for growing cancers. There				

is no evidence of repeatability in any other species, including humans. Studies on human populations concerned with the manufacture of Ti02 show no higher levels of lung cancer than the surrounding indigenous population.
However, should ECHA go ahead with the re-classification, I would like to point out some of the consequences of your action.
If I thought for a moment that the French request was justified, I would not be writing this. As a paint formulator, I would simply find another line of work and be grateful we had the foresight to save lives, including my own. You can take it therefore, I think the re-classification is simply wrong.
Others will no doubt deal with the genetics and chemistry, I want you to consider the consequences of re-classification.
Assuming you continue with risk-based assessment, the Ti02 becomes carcinogenic, as will anything containing Ti02, and, assuming treated articles also carry the classification, so will the walls of your offices, cars, football pitch white lines, road markings, most houses, a large proportion of the paintings in art galleries across Europe, make-up, sun-block, toothpaste and on and on.
Consider what will happen with the billions of litres of waste paint (would you want your house painted with a cancer causing agent?)and the tens, if not hundreds of thousands of jobs that rely, not just on making or applying paint, but those who sell it.
If we re-classify Ti02, the rest of the world would look at us and laugh and do their upmost to ensure it never reached GHS. Europe would be marooned (although it would be a dark maroon - no white additive), whilst the rest of the world carried on regardless.
Also consider the wealth of data we have gathered over years of use of these paints. This all becomes useless. Functional coatings, such as intumescent paints and anti-corrosion primers, will all have to be re-formulated and re-tested and our paint history would be wiped out. Essentially we would have to start from scratch.
I hope you reject the re-classification

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	IVP COATINGS	BehalfOfAnOrganisation	94

Comment received

IVP-Coatings represents the paint and printing ink industry in Belgium for more than 60 years, our members are under the largest users of titanium dioxide as a pigment. About 65 companies in Belgium account for a total of 3500 people directly employed and an annual turnover of 450 million euros.

We would like at this early stage alert the Authorities to the consequences of this proposed classification and labelling of titanium dioxide as carcinogen. Our members will feel a serious negative impact (non – availability of paint for consumers,..) as there are hardly any alternatives to titanium dioxide and they are relying heavily on the unique properties of titanium dioxide.
Moreover, in paint, titanium dioxide is embedded in a liquid matrix and is not available to exert inhalation toxicity (if toxicological effects should be confirmed) when the CLP regulation should implement a harmonised classification based on inherent properties.
We are as federation not aware of cases of cancer due to exposure of TI02 in product locations in Belgium and we believe that the consequences of the proposed classifications would be clearly disproportionate. The risks under discussion are based on dust exposure by inhalation (not only for titanium oxide dust) and should be tackled by appropriate risk

management options at the workplace.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Hungary	MAFEOSZ - HUNGARIAN PAINT PRODUCERS ASSOCIATION	BehalfOfAnOrganisation	95
Comment received				
MAFEOSZ is the Hungarian Paint Producers' Association, representing the specific professional interests of member companies since 1999. Providing representation of professional and economic interests of Hungarian paint producers, we would like to hereby express our concern regarding the potential carcinogen classification of TiO2 proposed by ANSES. During the years of our interest representation activities there were no cancer cases related to TiO2 usage in our member companies. TiO2 is one of the most important components of paint, and there is no replacement available. Classifying all forms of TiO2 as carcinogen would have a disproportional negative social and economic impact on our sector and the downstream users.				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	The Tobacco Industry Platform on REACH ("TIP")	BehalfOfAnOrganisation	96
Comment received				
The Tobacco Industry Platform on REACH ("TIP") is an industry group representing trade associations and companies involved in the manufacturing of tobacco products. The objective of TIP is to facilitate compliance with REACH and related EU legislation by TIP Members by notably addressing issues related to substances used in tobacco products. Members of the TIP contest the CLH proposal to classify all existing forms of titanium dioxide as Carc. 1B;H350 and believe that titanium dioxide should not be classified for any carcinogenicity hazard class based on the arguments detailed below: (i) The ANSES proposal reports under page 8 that "human data do not suggest an association between occupational exposure to TiO2 and risk for cancer". • The Guidance on application of CLP criteria stated that "substances are classified according to their potential to cause cancer in humans". • The most relevant animal model for humans is the human. The epidemiological data for various non-soluble particles (diesel exhaust, coal dust and titanium dioxide) have failed to find a significant correlation with particle exposure and cancer. • In 2011, NIOSH (National Institute for Occupational Safety and Health, April 2011) highlighted that "In general, the five epidemiologic studies of TiO2-exposed workers represent a range of environments, from industry to population based, and appear to be				

reasonably representative of worker exposures over several decade", and then concluded that "Overall, these studies provide no clear evidence of elevated risks of lung cancer mortality or morbidity among those workers exposed to TiO2 dust".
• In addition, a recent peer reviewed publication by Thompson and collaborators (Thompson et al., 2016) analysed epidemiological data that quantitatively characterize carcinogenic endpoints in humans, and concluded that "Considered collectively, this body of evidence in humans consistently reported a lack of significantly elevated risk of lung cancer in association with TiO2 exposure".

(ii) The ANSES proposal reports in page 67 that "there is sufficient evidence of carcinogenicity in experimental animals after inhalation". "Indeed, a causal relationship has been established between TiO2 and the increase of malignant lung tumours in female rats and benign lung tumours in males and female rats in 2 inhalation and 2 instillation studies".
• The Guidance on the application of CLP criteria states that "in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered".
• The anatomy of the lungs of rats and humans are fundamentally different and as such the location of the particulate matter accumulation in the lungs of rats is essentially different to that of humans, with the majority of similar sized non-soluble diesel particles in rats (up to 85%) being located in the alveolar and alveolar duct lumens and up to 91% of particulate matter in coal miners being located in the interstitium of the lungs, leading to different cells or particle-containing macrophages coming into in contact with particulate matter (Nikula et al., 2001). It is noted that "volumetric loading of macrophages and their subsequent inability to move and release of pro-inflammatory cytokines are key to the overload response" (Morrow, 1988) with humans having macrophages 4-times the volume of those in rats (Krombach et al.,1997) this implies that rat macrophages are more sensitive to lung overload than human macrophages (Nikula et al., 2001). Hence this could account for differences in responses seen in rats and humans.
• The ECETOC report (2013) discusses the rat model as being particularly sensitive to the development of pathological responses in the lung, and that these responses are not seen in other rodent models such as mouse or hamster.
• There is a lack of response in humans for PMNs (polymorphic neutrophils) in high dust exposed workers. PMNs are a critical part of the inflammatory response in the rat. The BALF biomarkers in human coal dust exposed workers corroborates the lack of carcinogenic response in the epidemiological data seen in humans (Morfeld et al., 2015).
• Another point of attention that does not support the classification according to CLP criteria is "the possibility of a confounding effect of excessive toxicity at test doses". Indeed, the neoplastic events observed in the Lee study (Lee et al., 1985) might be related to the fact that "rats uniquely respond to particle overload by exerting inflammatory and hyperplastic responses that are far more diminished in humans and non-human primates" (ECETOC, 2013; Thompson et al., 2016).
• Guidance on the application of CLP criteria for carcinogenicity clarifies that "some important factors which may be taken into consideration when assessing the overall concern are:…whether responses are in single or both sexes, whether responses are in single or several species" as these factors influence the overall likelihood that a substance poses a carcinogenic hazard in human.
• The study published by Lee and collaborators cited by ANSES, initially concluded that "an increase of bronchiolalveolar adenoma and squamous cell carcinoma occurred at 250 mg/m3" in female rats; yet a microscopic review of the lesions observed in this study was published in 2006 (Warheit et al., 2006), and most of the lesions were reclassified as non-neoplastic pulmonary keratin cysts.
• The second publication cited by ANSES to support the classification, is by Heinrich and

collaborators (Heinrich et al., 1995) but it is conducted only in female rats, and has not been reproduced in mice, and for this reason, it does not fulfill the CLP criteria for carcinogenicity classification.
• In both the Lee and Heinrich studies, both authors reported "impairment of [lung] clearance function".
• The Guidance on the application of CLP criteria states that "The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate."
• Further, the OECD Guidance on inhalation carcinogenicity studies (OECD, 2012) provides that "The use of concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged". The elimination half-time of titanium dioxide in the CLH report is in a range which OECD rejects for inhalation carcinogenicity studies.
• Finally, instillation is not a suitable dosing regime to reflect the exposure route relevant for humans. Human exposure will be lower doses spread over the course of the day, rather than a single large bolus dose. This method of dosing is predominantly recommended when the toxic potency for several materials are being compared (ECETOC, 2013).

(iii) In the summary and discussion on carcinogenicity (Par. 4.1.4), the ANSES proposal states that "even if several studies tend to demonstrate that the nano-form is more "reactive" (biologically active) than the micro-form, none was able to clearly correlate the hazard to specific forms or categories. In addition, carcinogenic effects were reported for nano and micro-forms. Classifying all the titanium dioxide particle sizes for carcinogenicity is therefore justified."
• Although the ANSES proposal reports that "Since TiO2 compositions vary in crystalline phase, morphology and surface chemistry (and all combinations thereof), the impact of variability of these characteristics on the hazard profile has to be considered", they also stated that several studies made distinction to potential effect to titanium dioxide in different forms: "a higher effect of nanoparticles in comparison to fine particles can be expected in the lung" "a higher carcinogenic potential of ultrafine TiO2 can be suggested" (page 50).
• The CLP Regulation provides that relevant information "shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used" and the Guidance on the application of CLP criteria also confirms that the physical form and particle size can have a significant impact on inhalation toxicity.
• Moreover, confounding elements are the coating of the crystalline forms, and impurities characterizing the test item, hence studies that do not specifically control for those variable could lead to biased results.

(iv) The ANSES proposal mentions in page 10 that "several notifiers titanium dioxide as a carcinogenic substance".
• According to the ANSES report, "several notifiers [classified] titanium dioxide as a carcinogenic substance, including the anatase forms". However, data available in the European Chemicals Agency (ECHA) databases demonstrate that only a minor percentage of notifiers have reported carcinogenicity classification:
• 4.39 % for titanium dioxide (CAS no 13463-67-7) (C&L inventory: 2688 notifiers proposed "not classified", only 9 notifiers used the Carc.1B;H350 and only 116 notifiers used Carc.2;H351) (ECHA, 2016a);
• 0.87% for rutile (CAS no 1317-80-2) (C&L inventory: 422 notifiers proposed "not classified", only 4 notifiers used the Carc.2; H351) (ECHA, 2016a);
• 1.42% for anatase (CAS no 1317-70-0) (C&L inventory: 149 notifiers proposed "not classified", only 3 notifiers used the Carc.2; H351) (ECHA, 2016a).

• In addition, titanium dioxide (CAS no 13463-67-7) (ECHA, 2016b) and rutile (CAS no 1317-80-2) (ECHA, 2015a) are registered substances under REACH for a high tonnage band. Altogether therefore, 132 registrants for titanium dioxide and one for rutile support the "no classification" based on 6 epidemiological studies and 12 carcinogenicity studies in laboratory animals. Not all of these studies were cited in the classification proposal.

In conclusion, available data used as evidence in the dossier submitted by ANSES on behalf of the French Member State does not support the proposed classification of titanium dioxide as a carcinogen category 1B, nor does it support a single classification of all forms of titanium dioxide.
Both epidemiological data and non-rat animal studies rather indicate that titanium dioxide is not a carcinogen and that any effects observed in rat studies are related to secondary mechanisms due to lung overload in the rat, which is known for its particular pulmonary sensitivity as compared to humans and other animals (rodent and non-rodent species).
Please note that study references quoted in these comments are provided in the attached document. Some of these references have not been addressed in the CLH proposal.

ECHA note – A non confidential attachment was submitted with the comment above.
TIP comments HCL proposal Titanium dioxide - 14072016.pdf

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	The Tobacco Industry Platform on REACH ("TIP")	BehalfOfAnOrganisation	97

Comment received

The Tobacco Industry Platform on REACH ("TIP") is an industry group representing trade associations and companies involved in the manufacturing of tobacco products. The objective of TIP is to facilitate compliance with REACH and related EU legislation by TIP Members by notably addressing issues related to substances used in tobacco products.
Members of the TIP contest the CLH proposal to classify all existing forms of titanium dioxide as Carc. 1B;H350 and believe that titanium dioxide should not be classified for any carcinogenicity hazard class based on the arguments detailed below:
(i) The ANSES proposal reports under page 8 that "human data do not suggest an association between occupational exposure to TiO2 and risk for cancer".
• The Guidance on application of CLP criteria stated that "substances are classified according to their potential to cause cancer in humans".
• The most relevant animal model for humans is the human. The epidemiological data for various non-soluble particles (diesel exhaust, coal dust and titanium dioxide) have failed to find a significant correlation with particle exposure and cancer.
• In 2011, NIOSH (National Institute for Occupational Safety and Health, April 2011) highlighted that "In general, the five epidemiologic studies of TiO2-exposed workers represent a range of environments, from industry to population based, and appear to be reasonably representative of worker exposures over several decade", and then concluded that "Overall, these studies provide no clear evidence of elevated risks of lung cancer mortality or morbidity among those workers exposed to TiO2 dust".
• In addition, a recent peer reviewed publication by Thompson and collaborators (Thompson et al., 2016) analysed epidemiological data that quantitatively characterize carcinogenic endpoints in humans, and concluded that "Considered collectively, this body

of evidence in humans consistently reported a lack of significantly elevated risk of lung cancer in association with TiO2 exposure".

(ii) The ANSES proposal reports in page 67 that "there is sufficient evidence of carcinogenicity in experimental animals after inhalation". "Indeed, a causal relationship has been established between TiO2 and the increase of malignant lung tumours in female rats and benign lung tumours in males and female rats in 2 inhalation and 2 instillation studies".
• The Guidance on the application of CLP criteria states that "in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered".
• The anatomy of the lungs of rats and humans are fundamentally different and as such the location of the particulate matter accumulation in the lungs of rats is essentially different to that of humans, with the majority of similar sized non-soluble diesel particles in rats (up to 85%) being located in the alveolar and alveolar duct lumens and up to 91% of particulate matter in coal miners being located in the interstitium of the lungs, leading to different cells or particle-containing macrophages coming into in contact with particulate matter (Nikula et al., 2001). It is noted that "volumetric loading of macrophages and their subsequent inability to move and release of pro-inflammatory cytokines are key to the overload response" (Morrow, 1988) with humans having macrophages 4-times the volume of those in rats (Krombach et al.,1997) this implies that rat macrophages are more sensitive to lung overload than human macrophages (Nikula et al., 2001). Hence this could account for differences in responses seen in rats and humans.
• The ECETOC report (2013) discusses the rat model as being particularly sensitive to the development of pathological responses in the lung, and that these responses are not seen in other rodent models such as mouse or hamster.
• There is a lack of response in humans for PMNs (polymorphic neutrophils) in high dust exposed workers. PMNs are a critical part of the inflammatory response in the rat. The BALF biomarkers in human coal dust exposed workers corroborates the lack of carcinogenic response in the epidemiological data seen in humans (Morfeld et al., 2015).
• Another point of attention that does not support the classification according to CLP criteria is "the possibility of a confounding effect of excessive toxicity at test doses". Indeed, the neoplastic events observed in the Lee study (Lee et al., 1985) might be related to the fact that "rats uniquely respond to particle overload by exerting inflammatory and hyperplastic responses that are far more diminished in humans and non-human primates" (ECETOC, 2013; Thompson et al., 2016).
• Guidance on the application of CLP criteria for carcinogenicity clarifies that "some important factors which may be taken into consideration when assessing the overall concern are:…whether responses are in single or both sexes, whether responses are in single or several species" as these factors influence the overall likelihood that a substance poses a carcinogenic hazard in human.
• The study published by Lee and collaborators cited by ANSES, initially concluded that "an increase of bronchiolalveolar adenoma and squamous cell carcinoma occurred at 250 mg/m3" in female rats; yet a microscopic review of the lesions observed in this study was published in 2006 (Warheit et al., 2006), and most of the lesions were reclassified as non-neoplastic pulmonary keratin cysts.
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• The CLP Regulation provides that relevant information "shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used" and the Guidance on the application of CLP criteria also confirms that the physical form and particle size can have a significant impact on inhalation toxicity.
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In conclusion, available data used as evidence in the dossier submitted by ANSES on behalf of the French Member State does not support the proposed classification of titanium dioxide as a carcinogen category 1B, nor does it support a single classification of all forms of titanium dioxide. Both epidemiological data and non-rat animal studies rather indicate that titanium dioxide is not a carcinogen and that any effects observed in rat studies are related to secondary mechanisms due to lung overload in the rat, which is known for its particular pulmonary sensitivity as compared to humans and other animals (rodent and non-rodent species). Please note that study references quoted in these comments are provided in the attached document to these comments. Some of these references have not been addressed in the CLH proposal. ECHA note – A non confidential attachment was submitted with the comment above. TIP comments HCL proposal Titanium dioxide - 14072016.pdf
Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	Cosmetics Europe	BehalfOfAnOrganisation	98
Comment received				
1. About Cosmetics Europe, the Cosmetics Industry and the importance of Titanium Dioxide in Cosmetic Products Cosmetics Europe is the European trade association representing the interests of the cosmetics industry. Its membership consists of 27 national associations of the EU Member States and beyond, 17 major international companies, four supporting association members, four supporting corporate members and three correspondent members associated members. Cosmetics Europe represents more than 4,000 companies throughout the EU via the active representation of its member national associations. For more information about "Cosmetics Europe", please consult our website: www.cosmeticseurope.eu The industry makes a significant contribution to the European economy across its value chain. It is estimated that the cosmetics industry brings at least €29 billion in added value to the European economy every year, of which approximately €8 billion is contributed directly by the manufacture of cosmetic products (the remaining €21 billion is generated indirectly through the supply chain). SMEs are key drivers of innovation and economic growth. While there are more than 5,000 enterprises manufacturing cosmetics in Europe, the vast majority of these companies are SMEs. In 2015, there were 4,605 SMEs in Europe. Along the value chain, a wide variety of different types of enterprises are involved indirectly in the cosmetics industry. For example, there are over 100 companies manufacturing cosmetic ingredients in Europe, 20,100 enterprises involved in the wholesale of cosmetics and 45,700 specialist stores retailing cosmetics. About half a million hairdressing and beauty salons (the majority of which are also SMEs or micro-enterprises) also rely on the use of cosmetics and the number of European spas is also growing and may be a source of inward investment to Europe in the form of "wellness tourism". The industry supports millions of jobs. Including direct, indirect and induced economic activity, the industry supports at least 2 million jobs. Of these, 152,000 workers are employed directly in the manufacture of cosmetic products, and around 1.6 million workers are employed indirectly in the cosmetics value chain.				

In cosmetics, Titanium Dioxide is widely used as colorant, as opacifier or as UV Filter and is chosen due to its efficacy and performance. Titanium dioxide is regulated under the European Cosmetic Products Regulation (EU CPR 1223/2009) as a cosmetic colorant (CI 77891, Annex IV) approved for all cosmetic products without any restrictions and as a UV filter (Annex VI) with a maximum concentration of up to 25%. Titanium Dioxide is one of the very few globally approved UV Filters / Sunscreen actives which are of relevance for global formulations.
Titanium dioxide is an important ingredient for the cosmetic industry. A search in the Mintel Global New Products Database (GNPD) indicated that over 20.000 cosmetics products launched the last 5 years contained Titanium Dioxide. This is over 10% of all European cosmetic product launches included in the database.
The use of TiO2 in cosmetic products is longstanding and an extensive toxicological data set is available. The safety of TiO2 has been acknowledged by a wide range of scientific and regulatory bodies throughout the world (e.g. EU EFSA, US FDA), resulting in their safe uses in various products including food products. For Cosmetic Products, the SCCS has reviewed and concluded on the safety of Titanium Dioxide on various occasions.

2. Impact of a CMR 1B classification on cosmetic industry
A classification of TiO2 as CMR 1B would mean that TiO2 is banned for use in cosmetics products. This follows from the European Cosmetic Products Regulation (EU CPR) which states in Article 15.2 that "the use in cosmetic products of substances classified as CMR category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008 (CLP) shall be prohibited". Exemptions to the CMR 1A and 1B ban are possible, however they can only be granted in very exceptional cases, when a series of stringent conditions are fulfilled (safety dossier, food compliance, no alternatives, specific uses…). In case an exemption would not be granted for use of TiO2 in cosmetic products, a very large number of cosmetic products would be impacted (see above, section 1).

Then, even in case an exemption would be granted to allow a particular use of CMR 1B classified TiO2 in cosmetics products, specific measures would be required during manufacturing (laid down by the Directive 2004/37/EC on carcinogens or mutagens at work):
(1) group protection equipment,
Massive investments would be needed to upgrade ventilation installation (i.e. from the delivery point of raw materials down to the evacuation stream of waste), either to fully close the TiO2 addition system or to bring the filtration standards to a minimum HEPA 14 efficacy.
(2) personal protection equipment,
The personal protection equipment would require major upgrades like the use of specific suits, masks, gloves, shoes, in combination with specific cleaning posts and procedures.
(3) waste management (solid and water effluents)
The waste management would need a specific approach to be aligned with waste treatment external partners.
(4) medical surveillance in our plants.
Medical surveillance of workers would be required in order to document their use of materials and their potential exposure to them.

3. Procedural Aspects
The classification proposal for TiO2 as Carc. Cat 1B – H350i requested by the French agency ANSES is based on evidence from two chronic inhalation studies (Lee et al., 1985; Heinrich et al., 1995) and two intra-tracheal instillation studies (Pott and Roller, 2005; Xu et al., 2010) performed in animals.
In addition, the CLH report refers to IARC classification of Titanium Dioxide ("IARC Group

2B" i.e. "possibly carcinogenic to humans") based on the above reported positive findings in rat carcinogenicity studies by the inhalation route (IARC, 2006). The relevance of these data are controversially discussed in the scientific community since > 30 years.

In other words, the submission of the CLH proposal by ANSES has not been triggered by any new data or any new concern. This proposed harmonized classification will be evaluated in line with the "application of the CLP criteria" as described in the ECHA guidance (Version 4.1-June 2015)
- 3.6.2.2., substances are classified according their potential to cause cancer in humans. In some cases there will be direct evidence on the carcinogenicity in humans from epidemiological studies. However, in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered.
- 3.6.2.3., Classification of a substance as a carcinogen requires expert judgement and consideration of many different factors (weight and strength of evidence).

Furthermore, TiO2 was put on the CoRAP list for evaluation in 2014 by France for the following ground of concern:
– CMR, suspected sensitizer;
– Exposure/wide dispersive use, consumer use, exposure of sensitive populations, high (aggregated) tonnage
The evaluation has been postponed until 2017.
Art. 48 of the REACH Regulation links the results of the substance evaluation to restrictions, authorization and harmonized classification and labelling.
As a result of the substance evaluation, the competent authority will consider how to use the information for the purpose of preparing a dossier for a CLH Proposal (former Article 115(1) of the REACH Regulation)
The substance evaluation is a tool to assess risks ("… [the] substance evaluation is primarily designed to clarify risks with risk management measures in mind." – ECHA Board of Appeals) whereas the CLH proposal is a risk management measure (RMM).
The CLH Guidance (Guidance on the preparation of dossier for harmonized classification and labelling, Version 2.0, August 2014) sections 4.1.1 and 5.2.2 reinforce the argument that information should be obtained through dossier or substance evaluation, before a classification proposal is made.
Therefore, the RMM should not precede the substance evaluation.

REFERENCES
Lee K.P, Trochimowicz H.J, Reinhardt C.F. (1985). Pulmonary response of rats exposed to titanium dioxide (TiO2) by inhalation for two years. Toxicology and applied pharmacology. 79(2): 179-92.

Pott F and Roller M. (2005). Carcinogenicity study with nineteen granular dusts in rats. European Journal of Oncology. 10(4): 249–81.

Xu J, Futakuchi M, Iigo M, Fukamachi K, Alexander DB, Shimizu H, Sakai Y, Tamano S, Furukawa F, Uchino T, Tokunaga H, Nishimura T, Hirose A, Kanno J, Tsuda H. (2010). Involvement of macrophage inflammatory protein 1 alpha (MIP1alpha) in promotion of rat lung and mammary carcinogenic activity of nanoscale titanium dioxide particles administered by intra-pulmonary spraying. Carcinogenesis. 31(5): 927-35.

ECHA note – A non confidential attachment was submitted with the comment above. TiO2_CE input CLHPublic consultation 14072016.pdf

Dossier Submitter's Response
See points 2, 3 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	TDMA/TDIC	BehalfOfAnOrganisation	99

Comment received

Industry Comment on behalf of TDMA/TDIC on the CLH Report for Harmonised Classification and Labelling
Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 Substance Name: Titanium dioxide
Date 13th July 2016

The Titanium Dioxide Manufacturers Association (TDMA) is a sector group of Cefic (the European Chemical Industry Council) and represents ten of the major producers of titanium dioxide (TiO2), and the entire 1,500,000 tonnes of TiO2 manufacturing capacity in Europe. The TDMA acts as the responsible voice of the TiO2 industry in Europe. The Titanium Dioxide Industry Consortium (TDIC) manages the REACH registration of titanium dioxide and related manufacturing process intermediates.

There is no other pigment providing opacity, durability, light scattering and UV absorbance similar to TiO2. Classification of TiO2 as Carc. Cat. 1B H350i would severely impact not only white products but also most opaque colours since TiO2 is also used in these. The presence in consumer goods would mean that do-it-yourself products such as paints, adhesives, sealants would no longer be available to the general public, requiring employment of professional users. Other uses such as food additives (E171) or cosmetics (sunscreens and others) would likewise no longer be possible. The implications for the entire minerals industry would be severe, since many industrial minerals (kaolin, bentonite, perlite, mica, diatomite, ball clays) contain TiO2 as a natural impurity up to 2% (w/w).

Introduction

The evidence presented in the REACH registration dossier of more than 130 co-registrants of titanium dioxide (EC No 236-675-5) supports a single registration as a mono-constituent substance of all forms of titanium dioxide and its hydrates, as described in the Substance Identity Profile (SIP), regardless of crystal phase, crystal size or surface treatment with no hazard classification.

The CLH Proposal for titanium dioxide submitted by The French Competent Authority (ANSES) has assessed the impact of the physico-chemical properties of the substance (size, crystalline phase, coating, shape) on carcinogenicity and concluded that there was no correlation between carcinogenicity and a specific form or category of the substance.

The proposed classification for titanium dioxide by ANSES as Cat 1B Carcinogen by inhalation (H350i) is "Based on available evidence and information in the registration dossier (e.g. mechanism of carcinogenicity, characterization of the particles) the proposed scope of the Annex VI entry is: All commercialized titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies". As our detailed comments

demonstrate, the inhalation carcinogenicity of Titanium dioxide, regardless of the route of exposure (oral, dermal or via inhalation) is not supported by conclusive and sufficient scientific evidence.

The formation of tumours upon inhalation exposure to TiO2 is considered specific only to rats, and limited to conditions of overload. This species specificity manifests itself by a complete absence of similar responses in all other tested species, coupled with negative human epidemiology, suggesting a lack of relevance of this observation to humans. In addition, the disposition of such inhaled particles has been shown to be substantially different between nonhuman primates and rats, with the latter being particularly sensitive. The lung cellular responses of rats exposed chronically to particles is hyper-inflammatory and hyperplastic, while primates show normal physiological reactions such as particle accumulation and macrophage responses to inhaled particles. The disposition of inhaled particles in cynomolgus monkeys and coal miners demonstrate that the majority of deposited inhaled particles migrate to interstitial compartments of the lungs, whereas these are retained primarily on alveolar surfaces in rats and subsequently stimulate active inflammatory responses.

There are five significant and interrelated factors that provide important insights into the fundamental differences in pulmonary responses between particle exposed rats and occupationally-exposed humans:

1. Interspecies differences in lung responses of rats versus other rodents, triggering different adverse outcome pathways (AOPs);

2. Interspecies differences in particle kinetics of rats versus nonhuman primates and humans triggering differential particle-related pulmonary responses;

3. Advanced and updated human respiratory tract models allowing more realistic particle translocation/retention estimates (and that correlate with morphometric assessments of lung responses to particles in monkeys and coal miners);

4. Differences in morphologies and characterization of rat vs. human pulmonary tumour types and locations within the respiratory tract; and

5. Comprehensive in-depth analysis of available epidemiological data from production workers exposed via inhalation to poorly soluble particles of low cytotoxicity (PSP) demonstrate no correlation between particle exposures and lung cancers or other non-malignant respiratory diseases.

TiO2 causes lung tumours in rats only under excessive overload conditions (i.e., 250 mg/m3) or at instillation of physiologically non-relevant high doses, which exceed the clearance capacity of rat lungs. Such conditions exceed the maximum tolerable dose and are therefore not suitable for CLP classification proposals, and also explicitly fall outside the validity boundaries of the OECD test guideline for inhalation carcinogenicity and ECHA's own guidance.

This "PSP overload" mode of action is restricted not only to TiO2, but extends to all other poorly soluble particles (PSPs) of low cytotoxicity, such as carbon black and coal mine dust. The animal laboratory toxicity profile for these analogous cases is similar, and the vast amount of negative human epidemiological data in coal miners underpins the lack of relevance of such findings in rats to humans.

We also highlight that hypothetical assumptions supporting the ANSES proposal without

the demonstration of any realistic possibility of harm, have been found to be insufficient evidence by the Board of Appeal of the European Chemicals Agency (for instance in the Decision in Case A-005-2014) and cannot be used as justification for the proposed classification of TiO2.

Finally, we challenge the assumption in the French Proposal that the classification of Titanium dioxide for mutagenicity is inconclusive. There is ample evidence in a wide range of assay systems as referenced in the REACH registration dossier of titanium dioxide to demonstrate that the substance has no primary genotoxicity, as particularly recently supported with the unequivocally negative outcome of the comprehensive NanoGenotox (2013) programme among others in micronucleus and transgenic mouse assays.

General comments

(a) Fundamental differences in pulmonary responses between particle-exposed rats and occupationally exposed humans (See also Annex1 for additional and specific detailed comments)

1. Interspecies differences in lung responses of rats versus other rodents
Throughout the CLH report, there does not appear to be a clear position on the mechanism of action: the relevance of lung particle overload is discussed only briefly, and despite clear indications of inter-species differences, the extrapolation of effects observed in rats to humans is postulated without scientific justification. Further, despite that it is mentioned that the underlying mechanism of TiO2-induced lung tumours specifically in rats is due to secondary genotoxicity via induced inflammation and ROS formation from inflammatory cells, it is nevertheless concluded that particle overload-induced lung tumours are transferable from rats to humans. The latter is in contradiction to the absence of any evidence of carcinogenicity in human epidemiological studies on TiO2 as well as in coal miners, the latter being affected by apparently heavy inflammatory lung conditions (pneumoconiosis) without correlation with lung cancer.

Data and findings from three subchronic, 90-day interspecies rodent inhalation studies provide convincing mechanistic justifications to better understand the distinct differences in cellular responses to particle overload exposures when comparing rats to either mice or hamsters (Bermudez et al., 2002; Bermudez et al., 2004; Elder et al., 2005; Carter et al., 2006). In addition, a conceptual AOP scenario has been developed (ECETOC, 2013) for the rat pulmonary response to particle-overload, leading to lung tumours which is substantively different from pulmonary responses demonstrated in particle-exposed mice or hamsters and/or in either nonhuman primates or coal workers. In chronic inhalation studies to TiO2 and carbon black particles, only rats developed tumours – but not mice exposed to the same particles/concentrations, despite the fact that their lung burdens and clearance kinetics indicated overload-based impaired clearance function.

Because of the experimental design, data from the 19-dust study of Pott and Roller (2005) for female rats cannot be interpreted in a manner that makes them useful for human hazard and risk assessment and development of airborne dusts limits in workplace environments. Likewise, because of the species (rat) and the exposure conditions (particle overload in the lungs), the data are not applicable to hazard classification of granular biopersistent particles (GBP) as to human carcinogenicity (Valberg et al., 2009).

There are two additional papers referenced in the CLH report as supportive and involve the use of intra-tracheal administration (p. 27-30). Xu et al. (2010) dosed HRas female transgenic rats multiple times by intra-tracheal instillation and observed increased DHPN-

induced alveolar cell hyperplasia and adenoma in the lung at the two doses administered. In a second, similar study with HRas transgenic male rats neither "micro" sized nor "nano" sized titanium dioxide caused any increased inflammatory changes or increased rates of adenoma/carcinoma after a single intra-tracheal administration (Yokohira et al., 2009). The CLH report acknowledges that there is little experience with the HRas rat model and intra-tracheal administration. There are no lung lesions without pretreatment with DHNP.
Consequently, these studies by Pott and Roller, Xu et al. and Yokohira et al. do not qualify as supporting evidence and should therefore be discounted.

2. Interspecies differences in particle kinetics of rats versus nonhuman primates and humans
Several 2-year inhalation studies compared the effects of similarly or identically exposed rats and monkeys to a variety of low solubility dusts, such as shale dust, petroleum coke dust and diesel exhaust particles (Wagner et al., 1969; Klonne et al, 1987; Lewis et al., 1989; MacFarland et al., 1982; Nikula et al., 1997; Nikula et al., 2000). In every case, the lung cellular responses of rats exposed chronically to particles were considered hyperinflammatory and hyperplastic, while the pulmonary responses in monkeys were limited to general, normal physiological effects (particle accumulation, macrophage responses) to inhaled particles. In addition, morphometric studies reported by Nikula et al., 1997 were developed to investigate the distribution patterns of inhaled particles in both chronically-exposed rats and cynomolgus monkeys. The results demonstrated that the majority of inhaled particles that deposited in the distal regions of the lung had transmigrated to interstitial compartments of the lungs of nonhuman primates. In contrast to the pulmonary responses and particle distribution patterns measured in monkeys, inhaled particles in diesel and coal dust exposed rats were retained primarily on alveolar surfaces, and subsequently stimulated active inflammatory responses. In another set of morphometric studies assessing the particle disposition pattern in deceased coal miners, particle distribution patterns similar to cynomolgus monkeys were measured. In this regard, most of the coal particles had translocated to interstitial sites (Nikula et al. 2001).

The relevance of particle-overload related lung tumours in rats for human risk assessment following chronic inhalation exposures to poorly soluble particulates (PSP) of low cytotoxicity has been a controversial issue for > 30 years. In 1998, an ILSI (International Life Sciences) Working Group of health scientists was convened to address this issue of applicability of experimental study findings of lung neoplasms in rats for lifetime-exposed production workers (ILSI, 2000). A full consensus view was not reached by the Workshop participants, but it was generally acknowledged that the findings of lung tumours in rats following chronic inhalation, particle-overload PSP exposures were unique to rats; and that there was an absence of lung cancers in PSP-exposed production workers. Subsequently following up on this, a further thorough and comprehensive review of the health effects literature on poorly soluble particles/lung overload was published by an ECETOC Task Force in 2013. One of the significant conclusions derived from that technical report specified that the rat represents a uniquely sensitive lung tumour model under chronic inhalation overload exposures to such PSPs.
Consequently, the unique pulmonary reactions in long-term inhalation studies in rats are fundamentally different in particle reaction and deposition compared to nonhuman primates and coal workers.

3. Use of advanced/updated human respiratory tract models allowing particle translocation/retention estimates
The ICRP – Human Respiratory Tract Model has been an internationally recognised standard model to estimate the deposition, clearance and retention patterns for workers

in the nuclear and coal dust industry (ICRP, 1994). The model has been updated/revised by Gregoratto and coworkers (2010; 2011) to demonstrate that a greater proportion of inhaled low solubility dusts translocate from alveolar/respiratory bronchiolar sites of initial particle deposition to interstitial sites. This updated revision has important implications for lung clearance and retention estimates of inhaled particles, and supports species differences in particle distribution patterns, in particular the finding of enhanced translocation to the interstitium. The impact of the model supports increases in the retention time of particles in the human lung. It is also noteworthy that the finding of enhanced transmigration rates in these models also correlates well with the morphometric findings reported by Nikula et al. (2001) in particle-exposed nonhuman primates and coal workers.
Consequently the ICRP model has been updated to include enhanced translocation of particles to interstitium which correlates with the morphometric data in nonhuman primates and coal workers.

4. Differences between rat and human pulmonary tumour types and locations within the respiratory tract
Fundamental differences have been recognised by human and veterinary pathologists when considering the characterisation and location of tumour types in rats chronically exposed to PSPs of low cytotoxicity vs. humans exposed to cigarette smoke or asbestos fibres (Schultz, 1996; Green, 2000). First, PSP-induced rat neoplasms are unique species-specific entities that are only consistently observed in particle overload instances. Furthermore, there is no known documentation of human production workers developing an increase in lung cancers following exposure to poorly soluble particulates. Moreover, the types of lung tumours characterised in humans exposed to cigarette smoke or asbestos fibres – occur primarily in the bronchiolar regions of the respiratory tract and do not have the "squamous or keratinising" features of rat lung tumours, which are more prominent in this region of the lung following chronic exposures to PSPs of low cytotoxicity. It generally is acknowledged that comparing asbestos and cigarette smoke-induced tumours in humans to PSP-induced neoplastic entities in the rat probably does not contribute meaningfully to cancer risk of such PSPs, as the lungs differ in morphological aspects such as the presence (humans) and absence (rodents) of a respiratory bronchiole (Schultz, 1996). Nonetheless, it should be recognised that cystic keratinising tumours of rats arise very differently than squamous lesions in humans and appear to be adaptive versus true neoplastic changes. An international panel of medical and veterinary pathologists was convened and agreed that the cystic keratinizing lesions were not malignant neoplasms, and that the most appropriate morphologic diagnosis for these lesions was "proliferative keratin cyst" (PKC) (Carlton, 1994; Levy, 1994). In the Lee et al. study 1985 – in which rats developed tumours after being exposed to 250 mg/m3 (but not at 50 mg/m3), it was noted by Lee that the lung tumours were different from common human lung cancers in terms of tumour type, anatomic location, tumorigenesis and were devoid of tumour metastases. Therefore, the biological relevance of these lung tumours was deemed irrelevant.

In the aftermath of two international pathology workshops (Carlton, 1994; Levy, 1994) designed, in part, to establish histological criteria for classifying pulmonary keratin lesions, these lesions were evaluated by four pathologists using current diagnostic criteria. Microscopic review of 16 proliferative squamous lesions, previously diagnosed as cystic keratinizing squamous cell carcinoma in the lungs of rats from the 2-year inhalation study was performed. Unanimous agreement was reached as to the diagnosis of each of the lesions. Two of the lesions were diagnosed as squamous metaplasia and 1 as poorly-keratinizing squamous cell carcinoma. Most of the remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts (Warheit and Frame, 2006).
Consequently, pathological analyses of lung tumours in rats exposed to PSPs of low

cytotoxicity versus human exposed to cigarette smoke and asbestos demonstrate different lesion types and locations in the respiratory tract.

5. Analysis of available epidemiological data from workers exposed via inhalation to poorly soluble particles of low cytotoxicity

All of the published epidemiological studies on titanium dioxide production works (Boffetta et al. 2004; Chen and Fayerweather, 1988' Ellis et al., 2010 and 2013; and Fryzek et al. 2003), carbon black and toner production workers demonstrate no association between working life-time exposures to PSPs of low cytotoxicity and lung cancer and/or non-cancer respiratory disease.
The relevance of the cited epidemiological studies is downplayed in the CLH report because of claimed "methodological limitations" and "misclassification of exposure". It is our opinion that the stated limitations are either only minor or even irrelevant, and do not effectively leave the conclusion of these studies in doubt.
What is of major concern is that the CLH report without obvious reason does not mention the recent cohort study (Ellis et al, 2010; Ellis et al, 2013) of TiO2 manufacturing workers (involving more than 5000 workers) which like all other previous studies does not indicate any association between TiO2 exposure and human lung cancer, despite the fact that these studies are referenced in the REACH dossier for titanium dioxide. In total, all available human cohort studies amount to a worker population of more than 24,000. Consequently, numerous epidemiological studies of more than 24,000 workers demonstrate no correlation between long-term exposure to TiO2 and lung tumours, and this is supported by two large case-control studies that included over 2000 lung cancers.

(b) Lack of evidence of a primary genotoxic mechanism of action for titanium dioxide (see also Annex 1 for additional and specific detailed comments)
The CLH report states that only few studies on bulk titanium dioxide materials are available. However, to reduce the number of references (stated reasoning: "Due to the high number of in vitro genotoxicity assays found, an exhaustive reporting of studies was judged neither feasible nor of any added values"), the authors decided to disregard all in vitro references published before 2010. We note that this approach does not comply with the legal requirements as laid down in the CLP regulation (Article 37(1) in conjunction with Annex VI, Part 2 and regulation 1907/2006 Annex I, Section 1-3), whereby:

1. "any relevant information from registration dossiers shall be considered and other available information may be used" (CLP, Annex VI, Part 2)

2. "the evaluation of nonhuman information shall comprise the hazard identification for the effect based on all available nonhuman information" (REACH, Annex I, Section 1.1)

The omission of relevant information solely on the basis of the publication date is clearly not in compliance with the legal requirements. It is further noted that the majority of data relating to the genotoxicity of bulk titanium dioxide was published prior to 2010, and was therefore inappropriately dismissed in the CLH report.
In addition, the studies presented in the genotoxicity annex were not rated according to their relevance, reliability and adequacy (as foreseen in the ECHA guidance Chapter R.4: Evaluation of available information, in conjunction with the Guidance on the preparation of CLH dossiers, Chapter 5.3). Without such rating, a balanced evaluation of the information against the classification criteria is not possible.
While the CLH report fails to identify any correlation between different forms of titanium dioxide and potential carcinogenicity, it cites several publications targeting nanoforms, seemingly reporting the presence of TiO2 nanoparticles within cell nuclei. However, the possibility that these particles are either overlying the nucleus in the sections used or

were transferred from cytoplasm to nucleus during sectioning (as is considered highly likely by experts in this technique) is very likely. In all reviewed papers, there is no direct evidence of naoparticles binding to DNA. Even if particles do penetrate the nucleus, oxidative damage is the only established genotoxic consequence of exposure to TiO2 nanoparticles. Extensive transgenic mouse testing was conducted within the Nanogenotox (2013) programme, and the results indicate that primary genotoxic effects can clearly be ruled out.

(c) Noncompliance with ECHA guidance (See also Annex 1 for additional and specific detailed comments)
The CLH report does not comply with ECHA Guidance on the preparation of dossiers for harmonised classification and labelling (Version 2.0, August 2014), in particular: (a) a relevance, reliability and adequacy screening was either not performed (or not documented transparently) on the references/studies, and (b) new human epidemiological evidence (also reported in the TiO2 dossier) was not considered (Ellis study), and (c) the database used for the assessment of genetic toxicity is incomplete.
The Lee et al. (1985) study used test item concentrations of 0, 10, 50, 250 mg/m³ for the chronic whole body inhalation exposure towards pigmentary titanium dioxide. The adequacy of the Lee et al. study (1985) needs to be evaluated for the purposes of carcinogenity classification. Adequacy defines the usefulness of information for the purpose of hazard and risk assessment; in other words whether the available information allows clear decision-making about whether the substance meets the criteria for classification.

The highest concentration used in the Lee et al. study clearly exceeded the maximum tolerated dose (MTD), as defined by an exceedance of physiological clearance mechanisms), since lung overload conditions were apparently already achieved at the concentrations of 10 and 50 mg/m³, as cited in the publication of the study director (Lee et al. 1986):

"Lung response at 10 mg/m³ satisfied the biological criteria for a "nuisance dust," while adverse effects resulting from gradually accumulated particles (8.1% lung dry weight, 67.7 mg per lung) were found after 1 year of exposure to 50 mg/m³. An early pulmonary response indicating an overloaded lung clearance mechanism (by the deposition rate exceeding the clearance rate) was manifested by massive accumulation of dust-laden macrophages (dust cells), foamy dust cells, free particles or cellular debris derived from disintegrated foamy dust cells in the alveoli adjacent to the alveolar ducts. Alveolar proteinosis also appeared to be an important marker of an overloaded lung clearance mechanism and was observed at 50 and 250 mg/m³ after 1 year of exposure."

In their Current Intelligence Bulletin document, NIOSH (2011) questioned/dismissed the relevance of the results following the exposures to 250 mg/m³ of the 2-year study. Moreover, Lee et al. commented that the relevance of these rat tumours for humans was negligible, due to anatomic type, location, etc. At the 50 mg/m3 exposure levels, there were no tumours in either male or female rats and this represented 118 mg/lung in the males and 130 mg/lung in the females. Therefore this study should not be considered a positive study for carcinogenicity – but instead a negative study for carcinogenicity in rats – because exposures to 50 mg/m³ for 2 years and lung burdens ranging from 118 mg/lung and 130 mg/lung did not produce tumours.

According to the NIOSH Executive Summary of their Current Intelligence bulletin; the 250 mg/m³ concentration in the Lee et al., 1985 study was an excessive dose and is not relevant for human risk assessment: as stated in that bulletin - "However, exposure concentrations greater than 100 mg/m3 are generally not considered acceptable

inhalation toxicology practice today. Consequently, in a weight-of-evidence analysis, NIOSH questions the relevance of the 250 mg/m3 dose for classifying exposure to TiO2 as a carcinogenic hazard to workers and therefore, concludes that there are insufficient data at this time to classify fine TiO2 as a potential occupational carcinogen."

The ECHA guidance on the Application of the CLP Criteria (Version 4.1, June 2015) highlights that "Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard" (section 3.6.2.3.2., p.379-380).

The CLH report also fails to consider recent (negative) human epidemiological evidence (Ellis et al., 2010 and 2013), despite this being reflected in the current REACH registration dossier for TiO2.
Finally, the database used for the assessment of genetic toxicity is incomplete, by explicitly limiting its assessment of in vitro data to the period 2010-2015, and thereby ignoring in vivo and in vitro data published prior to this period as well as data included in the TiO2 REACH registration dossier.
Consequently, the CLH report does not comply with current ECHA Guidance on the preparation of dossiers for harmonised classification and labelling.

CONCLUSIONS
It is the opinion of TDMA/TDIC that the current CLH report reflects an inaccurate and misleading picture of the alleged inhalation carcinogen hazard presented by titanium dioxide. This opinion is based on the following key issues as presented in more details in the Specific Comments section of our document:

• Due to significant and recognized deficiencies, the intratracheal instillation studies referenced by the CLH report do not qualify as supporting evidence and should therefore be discounted.

• Interspecies differences in lung responses of rats versus other rodents, triggering different AOPs and demonstrating that the rat is uniquely sensitive.

• The CLH report fails to recognize and assess the importance of the unique pulmonary reactions in long-term inhalation studies in rats that are fundamentally different in particle reaction and disposition compared to coal workers and nonhuman primates.

• The CLH report fails to recognize the critical importance of enhanced translocation of particles to the lung interstitium, which correlates with the morphometric data in nonhuman primates and coal workers and differs from that of the rat. This difference is clearly demonstrated by the internationally recognized and accepted ICRP Human Respiratory Tract model.

• The CLH report fails to recognize the pathological analyses of lung tumours in rats exposed to PSPs of low cytotoxicity versus humans exposed to cigarette smoke and asbestos, which demonstrate different lesion types and locations in the respiratory tract.

• The CLH report also fails to adequately assess the importance of the numerous epidemiological studies of more than 24,000 workers that demonstrate no correlation between long-term exposures to titanium dioxide and lung tumours or other chronic lung disorders.

• The CLH report does not adequately assess the available genotoxicity database that demonstrates a lack of a primary genotoxic potential for titanium dioxide.

• The CLH report does not comply with current ECHA Guidance on the preparation of dossiers for harmonised classification and labelling. It relies on studies using excessive doses; it fails to consider recent (negative) human epidemiological evidence, although reported in the REACH Registration dossier; and it fails to adequately assess the genetic toxicity database by explicitly limiting its assessment of in vitro data to the period 2010-2015, thus ignoring in vivo and in vitro data published prior to this period as well as data included in the TiO2 REACH registration dossier.

It is the opinion of the TDMA/TDIC that the CLH report has failed to provide adequate, sufficient or reliable information to warrant a classification of titanium dioxide for carcinogenicity.

ECHA note – A confidential and a non confidential attachment were submitted with the comment above.
TDMA-TDIC CLH commentary_Confidential attachment.pdf
TDMA-TDIC CLH commentary_Public attachment.pdf

Dossier Submitter's Response

See points 2, 3, 4 and 5 of the attachment to the RCOM.

Specific response:

- please note that the Board of Appeal Case A-005-2014 is not related to TiO2 and/or to classification process. Therefore, reference to this case is not applicable to the CLH report on TiO_2.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Croda Europe Ltd.	BehalfOfAnOrganisation	100

Comment received

After a full review of the information provided, Croda are in full support and agreement with the TDMA/TDIC position of no classification for Titanium Dioxide.

In our view, doubt has been cast on the suitability of the data to determine a true classification, in particular the inhalation data (potential overload of lungs: are high dose tumours actually relevant to humans? The justification is not clear).

Titanium dioxide is supplied for use as a broad spectrum UV filter in sunscreens and other cosmetic formulations. By absorbing and scattering light in the UVA, UVB and HEV region, titanium dioxide effectively protects against sunburn/blistering, photosensitivity, and skin cancer. It is the broad spectrum activity and toxicological profile (skin irritation / sensitisation etc.) of titanium dioxide that often make it a preferred UV filter, especially in baby formulations. Reclassification to a category 1B carcinogen based on questionable data could pose a significant risk to human health. Not only is titanium dioxide used as a UV filter in its own right, it is often added to formulations containing organic UV filters to boost efficacy.

The SCCS consider titanium dioxide safe for use in its intended application. However,

portrayal of the situation in the media cannot be controlled. Consumers are increasingly rejecting ingredients based on media coverage (preservatives), and the use of generic terminology, even though these ingredients have been assessed and deemed safe by an independent group of scientific experts (SCCS). Titanium dioxide brings many benefits to consumer health. Classification when doubt has been cast on the suitability of the data could pose a significant risk to consumer health.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Merck	BehalfOfAnOrganisation	101
Comment received				
Merck is a manufacturer and downstream user of titanium dioxide. Titanium dioxide is used by Merck in a broad range of different products – as such as well as in formulations. Main product categories are pearl effect pigments, functional fillers, functional materials and inorganic UV-filters. Our overall production volume of titanium dioxide is significantly above 1000 t/year and titanium dioxide is used in roughly 800 different products. Our products are used in various applications as e.g. automotive coatings, technical coatings, plastic master batches, cosmetic and pharmaceutical formulations (e.g. pearl effect pigments, UV filter, functional fillers) and food – just to name the most important applications. These are highly specialized application areas where a substitution is hardly possible – due to the excellent properties of Titanium dioxide. Titanium dioxide is a key component of our products – in case of a classification as a carcinogen (cat 1B) all of these products would be at risk because in some areas such a classification is directly related to a ban of these products (e.g. cosmetic products) and in all of the other it is very likely that the downstream users/the market will not accept using cmr classified products in their applications. Within the respective Merck business unit overall around 1000 employees are currently employed – 500 of these in the production plants. Based on an experience of over 60 years of handling titanium dioxide in powder form we are not aware of any relation to the development of cancer in this group. In addition we didn't get any feedback from downstream users indicating any carcinogenic effects due to handling of our titanium dioxide containing products. Merck is deeply concerned about the proposal for classifying titanium dioxide as carcinogen (cat. 1B). Taking into account the above described importance of titanium dioxide for our product portfolio, the economic impact also for our downstream users and the from a scientific point of view not comprehensible reasoning for the proposed classification Merck's position is "no classification of titanium dioxide". Merck agrees to and fully supports the TDMA/TDIC as well as the VCI position "no classification of titanium dioxide" – these industry associations provide in their comments comprehensive reasoning why the classification of titanium dioxide as carcinogen cat. 1b is considered to be not adequate.				

Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Canada	Canadian Paint and Coatings Association	BehalfOfAnOrganisation	102

Comment received

These comments are being provided by the Canadian Paint and Coatings Association (CPCA) in response to the European Chemicals Agency's (ECHA) open public consultation on the proposal from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) to classify all forms of titanium dioxide (TiO2) as a Category 1B carcinogen, by inhalation.
CPCA submits these comments on behalf of Canada's major paint and coatings and adhesives and sealants manufacturers (http://www.canpaint.com/manufacturer/) and their industry suppliers and distributors across Canada (http://www.canpaint.com/supplier/), representing retail sales of approximately C$10 billion annually. CPCA is also a long-time member of IPPIC (International Paint and Printing Ink Council) and has been closely involved in the development and promotion of the various IPPIC programs, initiatives and policies within its membership.

CPCA fully endorses the Titanium Dioxide Manufacturers Association (TDMA) / Titanium Dioxide Industry REACH Consortium and the IPPIC comments. All comments dispute the evidence provided by ANSES, urge ECHA to consider additional facts and literature findings in the development of a final decision and disagree with the adoption of the ANSES proposal.

The ANSES proposal will have serious and far-reaching (technical and economic) implications not only for the paint and coatings and adhesives and sealants manufacturing industry in Europe but also in all of North America and elsewhere in the world, as well as in other industries, since there is no other alternative white pigment that can be readily used with such unique properties and performance, cost advantage and safety record. As a result of this proposal, the sales of consumer products will be compromised that will lead to large-scale trade disruption.

CPCA has been actively supporting the Canadian Chemicals Management Program (CMP) initiative by the Federal Government (Health Canada and Environment and Climate Change Canada), which uses a fact-based and risk-based approach. It has proven to be a very efficient process over the years to adequately protect human health and the environment. In contrast, the ANSES (and IARC) approach is solely hazard based, which ignore many human epidemiological study findings having fully demonstrated TiO2 safety among workers in the past. The IARC classification scheme and mechanism for identifying cancer hazard agents, has limited utility for identifying poorly soluble particles' carcinogenic risks in humans, particularly when there is a discrepancy between experimental carcinogenicity results in a uniquely sensitive species like rats. Any subsequent hazard-based legislation can be seriously disconnected from real life.

Additionally, the Canadian Federal Government, as part of the Challenge (CMP-Phase 1), has thoroughly risk assessed similar particulate materials as TiO2 (e.g. carbon black,

crystalline silica, and other pigments), which are used in liquid formulations and are completely embedded into polymer matrices, and concluded to low occupational or consumer health risks with no further risk management action.
http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/index-eng.php

In its Proposed Approach to address Nanoscale Forms of Substances on the Domestic Substances List (February 2015), Canada has proposed to exclude biological materials, polymers and organic and organo-metallic pigments and dyes, unless they are intentionally manufactured to exhibit one or more nanoscale properties that include release and subsequent exposure.

http://www.ec.gc.ca/lcpecepa/default.asp?lang=En&n=1D804F45-1

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

Please note that the web link does not work.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Netherlands	The Valspar (UK) Corporation Ltd	BehalfOfAnOrganisation	103

Comment received

Valspar appreciates the opportunity to comment on the French Agency for Food, Environmental and Occupational Health & Safety's (ANSES) proposal to classify TiO2 as a Carcinogen Category 1B under the CLP. Valspar is a manufacturer of paints and coatings for the consumer and industrial markets in the European Union. If adopted, the Classification, Labeling and Harmonization (CLH) proposal will have an unnecessary, adverse impact on our ability to provide coatings that are vital to the functioning of a modern society by potentially banning its use in "do-it-yourself" (DIY) products and leading to severe restrictions in industrial and professional markets.

Valspar fully supports the original determination by the Titanium Dioxide Manufacturer's Association (TDMA) that TiO2 should not be classified under the CLP. We believe that the conclusions drawn by ANSES, using ECHA's own standards, are incorrect and that TiO2 is not a human carcinogen. Imposing an incorrect classification on a material such as TiO2 that has a long and demonstrated history of safe use is misguided and diverts resources from addressing issues of greater concern.

Our analysis of the scientific limitations of ANSES's proposal and its socio-economic impacts is outlined below:

1. Comments on ANSES's Proposed Harmonized Classification of TiO2

a. The animal evidence cited in the CLH report is not adequate for classification purposes: Category 1B substances are presumed to have carcinogenic potential for humans, based largely on animal evidence. In the CLH report, the proposed carcinogen classification is primarily based on the observation of tumours in two rat inhalation studies: Lee, 1985 and Heinrich, 1995. However, both of these studies have significant methodological

deficiencies which make them of little utility for the purpose of hazard assessment.

Regarding the Lee et al. study:

• Tumours were only observed at doses that clearly exceeded the maximum tolerated dose (MTD), as stated by the study director. Additionally, the authors noted that, due to excessive loading in the lungs of rats exposed chronically at 250 mg/m3, the lung tumours were different from common human lung cancers in terms of tumour type, anatomic location, and tumourigenesis and were devoid of metastases.

• ANSES' interpretation of the CLP Criteria is flawed and contrary to ECHA Guidance: When evaluating animal carcinogenicity data, ECHA's Guidance on the Application of the CLP Criteria, Version 4.1 (June 2015) emphasizes that "Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses. Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans."

The ECHA guidance lists several effects resembling the hallmarks of the TiO2 rat lung overload phenomenon and suggests that tumours occurring under such circumstances are not relevant for humans. In order for chemicals to meet CLP criteria for carcinogenicity, they should possess intrinsic potential to cause tumours at "lower, less toxic doses". This criteria was not met in the Lee study since tumours were not observed at the two lower dose levels.

• This study was performed contrary to OECD Guideline 451 (OECD 2009) and associated guidance documents (OECD 2011), which caution against the use of doses that overwhelm pulmonary clearance mechanisms. OECD states that such doses "may lead to tissue responses that are specific to the species being tested", may "produce false positive results (because metabolic/homeostatic mechanisms are overwhelmed, etc.), which may be problematic in assessing risk in humans", and may compromise the validity of the study.

• The exposure level used in this study exceeds the current recommended limit exposure concentration of 100 mg/m3 for chronic inhalation studies by OECD: NIOSH in its Current Intelligence Bulletin declared that "because the tumorigenic dose of fine TiO2 (250 mg/m3) in the Lee et al. studies [1985, 1986a] was substantially higher than current inhalation toxicology practice—and because there was no significant increase in tumors at 10 or 50 mg/m3—NIOSH did not use the highest dose in its hazard identification and concluded that there is insufficient evidence to classify fine TiO2 as a potential occupational carcinogen."

• ANSES did not consider the impact of the reclassification of the lung lesions observed in Lee using modern criteria. Warheit and Frame, 2006, conducted a review of the 16 lesions observed in Lee at 250 mg/m3 using modern diagnostic criteria. Two of the lesions were diagnosed as benign squamous metaplasia and only one as a malignancy; a poorly keratinizing squamous cell carcinoma. The remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts which are a unique response of the rat lung to particle overload conditions. ANSES should have assessed if the reclassifications reported by Warheit and Frame changed the overall conclusion that TiO2 was carcinogenic. In the CLH report, the authors failed to address whether the reclassifications of the lesions changed the statistical significance of the study findings.

Regarding the Heinrich study:

• Heinrich was not a guideline study – it was performed only in females and the exposure concentration varied significantly during the experiment making it impossible to assess a dose response paradigm. For these reasons, this study was assigned a Klimisch Score 3 (i.e. not reliable) by ANSES.

• Furthermore, because the publication of this report preceded the international pathology workshops which revised the criteria for classification of cystic keratinizing squamous lesions of the rat lung, any conclusions about whether observed lesions were actually tumours should be deferred until the lung tissues can be re-evaluated using the revised criteria (just as Warheit and Frame did for the Lee study).

b. Significant limitations of the other supporting studies cited by ANSES: While the Lee and Heinrich studies were used by ANSES as the primary basis for its Carc. 1B classification, ANSES also lists several studies (Pott et al., 2005; Xu et al., 2010; and Yokohira et al., 2009) that employ non-physiological (intra-tracheal) administration routes to bolster its case. The CLH report neglects to address the limitations of such studies, which are unreliable since they are known to overwhelm normal lung defenses and activate mechanisms in the rat which are not relevant to human exposures.

As such, ECHA has stated that "Findings from studies using these [non-physiological] routes may provide useful information but should be considered with caution. Usually dosing via these routes provides a high bolus dose which gives different toxicokinetics to normal routes and can lead to atypical indication of carcinogenicity". (ECHA, 2015).

c. The claim that rat tumour responses in a lung overload context are relevant to humans is not supported by science: The CLH report asserts (on page 67) that "the [lung] overload concept seems to be relevant for humans (in particular for workers exposed to high dust exposure) since it appears that lung retention and chronic pulmonary inflammation in humans are consistent with findings in rats." This statement, aside from being incorrect, includes no references. Particle retention and clearance and the resulting response in the overloaded rat are fundamentally different than in humans exposed to high levels of dust.

Coal miners, a subpopulation known for significant exposures to dust, did not develop lung overload (i.e. the particle clearance rate was not impaired), even under high exposure conditions (Kuempel et al., 2001; Tran et al., 2000). In a recent technical report, ECETOC, 2013, makes the argument that "... [the model] provides rather strong indications that the overload concept as being described for rats is of little relevance for humans which have been chronically exposed to high levels of dust." (ECETOC, 2013).

While particle retention and chronic lung inflammation is able to occur in both rats and humans exposed to respirable particles, the responses at the molecular, cellular, and tissue level are species-specific, and have significant implications for disease outcome. For example, inhaled diesel soot is retained predominantly in the alveolar regions of rats, whereas similar particulates are retained primarily in the interstitial compartments in humans.

The differences between species may lead to distinctly different responses to the inhaled particles. In humans, clearance mechanisms remove particles to interstitial compartment of the lung where clearance is mediated by the lymphatic system. In the rat, however, retention in the alveoli leads to a sustained inflammatory/cytotoxicity response

corresponding to inflammation, fibro proliferative disease, cell proliferation, reactive oxygen-mediated genotoxicity and lung tumour development. None of these effects have been documented in particulate-exposed workers. (ECETOC, 2013)

ECETOC ultimately concludes "…tumours have to be considered the `adverse outcome` only in rats whereas non-neoplastic changes, e.g. fibrosis, seem to be the `adverse outcome` in other species." They credit the rat's unique response to factors such as "the diversity of toxification/detoxification systems, like anti-oxidants impacting the degree of resulting `oxidative stress`, apoptosis as well as DNA repair capacity." (ECETOC 2013).

In conclusion, for these reasons and others mentioned in the TDMA/TDIC Commentary, we support the TDMA/TDIC position of no classification of TiO2.

2. Exposures to TiO2 from Paint and Coating Applications are negligible

Free, unbound TiO2 is not present in either formulated coating products or in cured coating films. Therefore, classifying these products as human carcinogens based on animal studies conducted on unbound, fine particulate TiO2 is inappropriate.

The International Agency for Research on Cancer (IARC) in Monograph 93, recognized that TiO2 exposures from formulated paint and coating products are unique from exposures to free TiO2 in production and formulation operations by stating:

"Titanium dioxide is used in various industries (see Section 1.2.2) and exposure may occur before and during the addition of titanium dioxide to matrices such as paints, coatings, plastics, rubber, ink and foodstuffs. The potential for exposure is greatly reduced in other parts of the process….

No significant exposure to primary particles of titanium dioxide is thought to occur during the use of products in which titanium dioxide is bound to other materials, such as in paints."

In the United States, the state of California's Office of Environmental Health Hazard Assessment (OEHHA) took a similar approach towards bound TiO2 under the state's Safer Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). California listed TiO2 on its Proposition 65 list based on its IARC Group 2B designation, but limited the listing to "airborne, unbound particles of respirable size."

The positions of both IARC and OEHHA are further supported by recent studies which demonstrate that insoluble particulates such as carbon nanotubes, nano-silver, zinc oxide and nano-TiO2 are encapsulated in the paint film once the coating is dry. The vast majority of particles remain bound even after sanding or other abrasive operations (Gomez, 2014; Gohler, 2010; Saber, 2012a; Saber, 2012b).

3. Potential Regulatory Impacts on the Paint and Coatings Industry if the CLH Proposal is Adopted.
We do not believe that ANSE's proposed classification of TiO2 has been adequately justified. If finalized; however, the classification will likely have significant regulatory consequences under REACh, the CLP and Directive 2004/37/EC for the paints and coatings industry. These are detailed below:

a. The CLH proposal will prohibit the use of TiO2 in consumer paints and coatings under Annex 17, entry 28, of REACh: If the CLH proposal is adopted, consumer coating

products containing 0.1% or more of TiO2 may be subject to a ban in the EU under Annex XVII (Entry 28) of REACh. Since most architectural paint contains TiO2, paint and coating manufacturers would be forced to switch to other, less desirable pigments that will impact performance, cost and aesthetics.

b. Classification may lead to Authorization under REACh: If the CLH proposal is adopted as written, TiO2 will be considered a Substance of Very High Concern (SVHC) and thus be subject to the authorization rules under REACH. Simply having SVHC status will have significant market and stigmatization consequences. Paint and coating manufacturers will have to undertake resource intensive reformulation programs for existing products in anticipation that many uses of TiO2 will be either severely restricted or rejected by our customers.

The Authorization process for TiO2 will be exceedingly complex and expensive for both Industry and for ECHA due to the plethora of uses of TiO2. The evaluation and replacement process will ripple through the supply chain passing from manufacturers to coating suppliers to parts and components suppliers to finally the manufacturers of finished goods. All users of TiO2 (e.g. paints and coatings, plastics, paper, inks, textiles, electronics, food, cosmetics, and pharmaceuticals) will be impacted by the process and can be expected to file their own applications for Authorization.

c. Restrictions imposed by the Directive 2004/37/EC - Carcinogens or Mutagens at Work: Classification of TiO2 as a 1B carcinogen may invoke Directive 2004/37/EC requiring manufacturers, processors such as coating manufacturers, and downstream commercial users such as painters, to implement stringent workplace controls. The basic provision of the Directive is that "The employer shall assess and manage the risk of exposure to carcinogens or mutagens." Worker exposure is eliminated either by replacement with a safer alternative or the use of closed systems. If either is not practical, then the employer is obligated to take necessary measures to "reduce exposure to minimum."

The Directive was intended to control workplace exposures to genotoxic carcinogens and mutagens that are assumed to have no safe threshold for exposure. ANSES, as well as other reviewers, have determined that TiO2 is not a genotoxic carcinogen and that any effects in the rat are secondary to pulmonary inflammation; a threshold effect. Accordingly, we believe that the requirements that would be triggered by Directive 2004/37/EC are excessive and unnecessary for the protection of worker health.

Valspar manufacturing facilities in the EU already control employee exposure to TiO2. Large production facilities use enclosed silo system to distribute TiO2 in the plant. Smaller batches rely on Local Exhaust Ventilation (LEV) at the point of use to minimize exposure. Eye protection, dermal protection (gloves, Tyvek coveralls); showers and respiratory protection are provided. Annual lung function assessments are provided and regular occupational exposure monitoring is conducted in the plants.

Implementation of the Directive would impose significant costs to upgrade manufacturing facilities. Increased use of enclosed storage and distribution systems for TiO2 will be needed. Manual handling operations may require enclosure and/or improved local exhaust systems. Stringent exposure limits could require facility ventilation upgrades. Bags and other TiO2 contaminated waste would be considered hazardous requiring special disposal procedures.
Downstream Small and Medium Users (SMU's) such as professional painters would also be impacted. Many of the requirements of the Directive such as enclosing operations, equipment cleaning and waste disposal, workplace monitoring, and providing hygiene facilities are not practical for site applied coatings. The net result may be to indirectly

prohibit the use of TiO2 in professional coating markets as well.

In summary: We believe that the CLH proposal is based on a flawed interpretation of the scientific evidence and a misguided application of the CLP hazard criteria. The consequences of adopting the harmonized Carcinogen 1B classification would be devastating to many industries that rely on TiO2 despite overwhelming evidence of safe use in the workplace, the absence of adverse effects in exposed individuals, and negligible exposure to downstream users and the general public. For these reasons, we support the TDMA/TDIC position of no classification of TiO2.

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Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	The Little Greene Paint Company	BehalfOfAnOrganisation	104

Comment received

Dear Sir or Madam,

I represent The Little Greene Paint Company established in the United Kingdom and respond on behalf of that company. We are a formulator of high end decorative coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen.

I have been using this substance in my career for over 40 years with zero reports of problems or issues. My company currently employs 102 people and as we successfully manage our workplace exposure to dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.

TiO2 is a vital material used in manufacturing our products and all of the alternatives available fall a long way short of providing those same properties of opacity that an end user of paint products would consider acceptable as a replacement.

The proposed classification would result in Little Greene having to reformulate to a substantially worse product with lower opacity and in consequence this new product would require a greater proportion of precious raw materials than before to achieve the same opacity upon the wall, thereby increasing the environmental impact. Without the use of Titanium Dioxide in paints the vibrancy and opacity of colours would be reduced in the same way.
This significant and noticeable drop in performance would translate into a dramatic fall in sales for us which would inevitably lead to downsizing our staff across the UK, France, Germany Ireland and Holland.

Yours faithfully, <confidential>
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy	Federchimica	BehalfOfAnOrganisation	105
Comment received				
Federchimica is the Italian Federation of the chemical industry. At the present time 1400 companies, with a total of 90.000 employees, are part of Federchimica. They are grouped into 17 Associations, articulated into 41 product groups. Federchimica is a member of Confindustria (General Confederation of the Italian Industry) and CEFIC (European Chemical Industry Council). Titanium dioxide is very widely used by Federchimica'members and is included in numerous products and articles used by industrials, professionals and consumers. Federchimica welcomes the opportunity to comment on the Public Consultation on the HCL proposal for Titanium dioxide. The proposed classification and labelling for titanium dioxide by the French MSCA is inappropriate for the reasons reported below and would have serious and disproportionately negative impacts on the European and Italian market, regarding the products manufactured by our member companies. Some Italian Sectors involved in TiO2 use: Paints. Coatings and Inks TiO2 is an essential raw material for paint, coatings and ink industries, and is used in over 85% of this products. It's also widely used in adhesives. It provides key properties such as whiteness, opacity, brightness, protection from UV light, stability and durability. It is the most efficient and optimal way to provide an opaque white or coloured layer for decoration and protection for walls, metal objects, plastic films etc. At this time, there is no alternative that offers the same characteristics and advantages. The new classification proposed, in addition to the negative perception of the term "carcinogen," would result in the possible ban on the public sale of all TiO2-containing products to the consumer. Although the proposed classification relates to the inhalable fraction of TiO2, it would impact even on liquids and pastes containing TiO2 even though it is not available for exposure by inhalation (not breathable). Detergents TiO2 is present in certain detergent products at levels <1% (with majority < 0.1%) and is mostly used as an opacifier or as a stability coating for granular enzymes. Classification as a carcinogen would imply a ban for most detergents containing TiO2 because of mixture classifications and/or consumer perceptions that those products are now unsafe for use. TiO2 replacement for enzyme coating is not straightforward and will necessitate significant R&D work; there are replacements for the use of TiO2 as an opacifier although they may not have the same well-known safe environmental profile. The use of TiO2 in detergent products leads to insignificant consumer exposures via inhalation and replacements will not bring any consumer nor environmental safety benefits.				

Ceramics
TiO2 is used as a starting material for the synthesis of important inorganic coloured and white pigments (e.g. with rutile or anatase type structure) used in the field of ceramic frits and enamels (used in both industrial and consumer applications). Frits and inorganic pigments can be found in products with materials based on: glass, ceramics and metal applications. Typical concentrations of TiO2 in complex inorganic pigments are between 1 and nearly 100%. The typical concentration range in frits is between 3 – 20 % of TiO2. The TiO2 concentration in final mixture strongly depends on the application.
TiO2 is a pigment of extraordinary light fastness, a high refractive index and, at an optimal particle size distribution in the range of 0.2 - 0.35 µm, a very high light scattering capability. It has, therefore, the highest opacity among all white pigments as well as an excellent brightening capacity vis-à-vis coloured media. Furthermore it is important to emphasise that in the vast majority of downstream uses, titanium dioxide is bound in a matrix (e.g. ceramic tile), and thus not freely available.
We expect serious negative effects on this business since TiO2 will be stigmatized and, thus, - even if it legally could be used - it will be entirely banned in consumer applications/products. Some of the negative effects are: loss of business due to less market acceptance, a reduction of the variety in products and a significant disadvantage for EU business compared to non EU competitors. Because of these outstanding properties and the resulting performance there are no suitable available alternatives regarding health, safety, and environment.

Food Additives
In the food sector, titanium dioxide considered safe and it is used as a coloring additive and is identified by the e-number "E171". The European legislation on food additives has recently undergone a renovation and the specifications for titanium dioxide used as a food additive are laid down in Reg. 231/2012, while Reg. 1333/2008 (and its modifications) authorizes this additive with a quantum satis dose, in various types of foods.
The safety of titanium dioxide is also currently being reviewed, as part of the normal procedure of reevaluation of all food additives (Reg. 257/2010). The deadline for the publication of EFSA scientific opinion was 31 December 2015, but to date it has not yet been published.
Titanium dioxide is permitted as a food additive in Europe, USA and also by Codex Alimentarius (FAO/WHO) with a 1969 safety assessment (JECFA) and 1975 (SCF); in 2005, EFSA evaluated the safety of titanium dioxide in the "rutile" form, equivalent to the already used "anatase" (http://www.efsa.europa.eu/en/efsajournal/pub/163: The Panel concluded that the use of rutile titanium dioxide in the platelet or amorphous forms would not pose any safety concerns).

Plastics
Main fields of use are coating materials like varnishes and paints, followed by plastics colouring and laminated paper. Titanium Dioxide has prevailed as the leading white pigment. Its interaction with light is evident, firstly, as light scattering which leads to opacity or as absorption of the energy of UV light, in order to protect polymers from decomposition under UV light.
The photocatalytic property of titanium dioxide is used in some polymer products (e.g. self-cleaning plastic surfaces).
Regarding Titanium Dioxide in plastics, it has to be considered that this additive is firmly bound into the plastics matrix.
PlasticsEurope Italia wishes to point out the wide use of Titanium Dioxide in the polymer industry and the very significant impact on industrial and consumer products that could occur if the use of TiO2 were to be restricted. Because of the outstanding properties of

Titanium Dioxide regarding health, safety, environment and performance, no suitable alternatives are available.
PlasticsEurope Italia fully respects the scientific analysis that leads to hazard classification of substances, but requests that the most thorough possible processes are applied to the assessment in the case of TiO2 in view of its importance of to our industry.

Cosmetics
Impact on the cosmetic sector of TiO2 classification
TiO2 in different forms (nano, non nano, coated and uncoated) is used in many cosmetic products. It is authorized as colorant and as UV filter in cosmetic products (Annex IV and VI respectively, Regulation 1223/2009).
A CMR 1B classification of TiO2 would trigger a ban for the use in cosmetic products as cosmetic ingredient (art. 15 of Reg. 1223/2009).
Exemption to the CMR 1A/1B bans may only be granted in very exceptional cases, when stringent exemption criteria are fulfilled (art.15§ 2 Reg.1223/2009).

Justification to reject the French proposal
For the following reasons we consider the submitted proposal for a classification of titanium dioxide as carcinogenic category 1 B neither as justified nor as appropriated:

1. Safe use for many decades – Many large epidemiological studies of workers have shown no increase in risk of lung cancer in humans and no evidence indicating a "causal relationship" between exposure to TiO2 and development of lung cancer in humans.

2. Weak Weight of evidence of "lung overdose" studies in rats - The classification proposal in the CLH report is based essentially on studies in rats exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and the ECETOC Report unanimously observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons. Therefore, a classification is neither justified nor appropriate from the toxicological perspective.

3. Intrinsic substance property required - For identifying carcinogens, CLP requires intrinsic data as outlined in its annex and this is in line with the purpose, scope and application of globally harmonized system of classification and labelling of Chemicals (GHS). In its dossier, the French MSCA, stated by its own conclusion, that the potential inhalation health risk of titanium dioxide is linked to a substance independent property of dust. This is obviously not intrinsic. Therefore, a harmonised classification would be not the right measure to address their findings.

Additionally we explicitly support and refer to the detailed toxicological assessment of TDMA (Titanium Dioxide Manufacturer Association) and the TDIC (Titanium Dioxide Industry Consortium).

Conclusion
Titanium dioxide is safely used chemical products and the large body of data on TiO2 demonstrates that it does not present a cancer risk for humans via any exposure routes and the classification criteria for carcinogenicity are not met.
The proposed classification and labelling for titanium dioxide by the French MSCA would have serious and disproportionately negative impacts on the Italian market regarding the products manufactured by our member companies and would not contribute to enhanced protection of health and environment. No suitable alternative with the same performance in appropriated quantities is available. Thus the consequences in the supply chain would

be dramatic.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99. Regarding EFSA conclusion, please note that only carcinogenicity by oral route was assessed. Furthermore, regarding cosmetic uses, the SCCS does not recommend "the use of nano titanium dioxide in spray applications that could lead to exposure of the consumer's lungs to nano titanium dioxide by inhalation" due to potential carcinogenicity.
RAC's response
Noted. RAC concluded that the TiO2 profile of lung carcinogenicity is specifically linked to the inhalation route. Available data with oral and dermal exposure did not result in TiO2 carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria	Pipelife GesmbH & Co KG	BehalfOfAnOrganisation	106
Comment received				
General Comment Pipelife Austria GesmbH & Co KG: We are plastic pipe producer for sewage, cable protection and pressure pipes, processed materials are PVC, PE and PP. We are using in our formulations Masterbatch for coloring where pigments are in use with titanium dioxide as raw material. I respond on behalf of Pipelife Austria, we are deeply concerned about the proposal made by France (ANSES) for classifying titanium dioxide as a carcinogen. We have been using Masterbatch where titanium dioxide is used for decades. Based on many years of experience using these Masterbatches we are not aware of any relation to the development of cancer by our workers. There has never been found any health risk processing Masterbatches with titanium dioxide inside and no statistical data give any indication in this direction. It is not suitable to overestimate animal studies to a realistic and practical long term experience. Titanium dioxide is one of our key material for coloring our products. The proposed classification would also affect all chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Due we are downstream users of titanium dioxide as pigment in the used masterbatch we would have to face a direct or indirect economic loss because there is no economic substitution available on the market. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy	AVISA/FEDERCHIMICA	BehalfOfAnOrganisation	107
Comment received				
'I represent a Company established in the EU Member State ITALY and respond on behalf of that company. We are a formulator of Printing inks and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 115 people. We have been using this substance for 60 years. As we successfully manage the workplace exposures of dust,the use of efficient ventilation and extraction and other risk management measures , when handling any material that may be considered a dust hazard. We believe that it is important that this is a generic dust-related statement, rather than specifically related to TiO2 and the classification discussion;we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market that the health concern is related to the inhalation of dust yet, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach, all finished liquid products based on TiO2 would be affected by this new classification; and to our company'the extent to which your business depends on TiO2, that there is no direct replacement for this substance in coatings and inks, and the perceived impact if the French proposal is supported. This could include mention of the resultant ban on the sale of all decorative wall paints and white DIY products to the general public, the introduction of additional measures related to worker safety and product labelling , and legislatively pressure (through REACH and / or the Carcinogen & Mutagens Directive) to replace TiO2 in all our products.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	GAMA-Global Acetate Manufacturers Association	BehalfOfAnOrganisation	108
Comment received				
GAMA (Global Acetate Manufacturers Association) is the global association representing the major cellulose acetate manufacturers, including the manufacturers of acetate tow, a raw material used in manufacturing cigarette filters and acetate yarn used in the textile apparel market. The organisation was established to enhance the long-term viability of cellulose acetate and its derivative products on a worldwide basis. GAMA's mission is to advance, develop and promote these products, and to jointly address the challenges the industry faces. GAMA has members with production sites in Lanaken, Belgium (Celanese), Freiburg, Germany and Roussillon, France (Solvay), as well as production sites outside of the European Union. Titanium dioxide (TiO2) is used by GAMA's members at relatively low levels as a delustering agent in the production of cellulose acetate tow and cellulose acetate yarn. Cellulose acetate tow is then used in the manufacturing of cigarette filters. Cellulose acetate yarn is a fiber used in various textile applications, such as apparel. Over the past				

50 years GAMA members have safely used titanium dioxide in their production processes. Titanium dioxide has unique refractive properties in these applications to which there are currently neither economic nor functionally viable alternatives available.

GAMA believes that titanium dioxide should not be re-classified as "potentially carcinogenic to humans" (category 1B) / "may cause cancer by inhalation" (H350i). GAMA also believes that titanium dioxide does not meet the carcinogenic criteria as set out in the Classification, Labelling and Packaging regulation ((EC) No 1272/2008). The proposal by the French agency "Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail" (ANSES) to re-classify titanium dioxide is not well-founded. The data provided in the scientific comments "CLH report Proposal for Harmonised Classification and Labelling" submitted by the Titanium Dioxide Manufacturer's Association (TDMA) and the comments submitted by Verband der Chemischen Industrie (VCI) indicate the current 'no classification' of titanium dioxide is the correct classification.

Dossier Submitter's Response

See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Huntsman Pigments and Additives	BehalfOfAnOrganisation	109

Comment received

Huntsman fully endorses the scientific data and comments submitted by the TDMA and TDIC on behalf of the industry. The classification proposed is not justified.
Titanium dioxide is ubiquitous in modern society providing whiteness and opacity in a vast range of products such as paints, plastics, textiles, inks, papers and many others. As well as providing colour it helps protect from UV light preventing embrittlement, fading and cracking in polymers and in paints or other coatings. Titanium dioxide is therefore an important contributor to sustainability in that it helps ensure the longevity of plastic items (such as window frames) and increases the lifetime of the substrates onto which paint is applied (e.g. steel infrastructure, pipelines etc). When used indoors it increases luminosity reducing the energy requirements from lighting. From a societal point of view, it has also been used for many years to help protect against skin cancer when used in sunscreens.
As a manufacturer of titanium dioxide for over 80 years we have seen no evidence of cancer linked to worker exposure at any of the factories we have operated around the world, nor are we aware of any down the very extensive supply chain. These observations are in accord with the extensive epidemiological studies carried out across the industry.
In practice, we consider titanium dioxide to be one of the most highly tested chemicals of all time. It has been used in a massive range of products including in foods, cosmetics and pharmaceuticals that themselves require continual stringent testing. From a scientific point of view, titanium dioxide has typically been used as an inert control in experiments with no evidence that implies a cancer effect in humans.
The French Proposal states that:

(page 7) "In the current REACH registration database there is one registration for 'titanium dioxide' with 130 members in April 2016. This registration stated that it intends to cover 'all crystal phases & hydrates of titanium dioxide including rutile, anatase, monohydrate and dihydrate'. However, the types and number of compositions considered to be covered in terms of crystalline phase, morphology and surface chemistry are not

transparently (and exhaustively) reported. Due to this lack of transparency, the impact on the hazard profile when the parameters vary cannot be established from the information included in the registration dossier. However it is clearly stated in the registration dossier that all possible variations are considered equivalent in terms of hazard profile. Taking these statements into account, the approach applied in the REACH dossier was used to support the scope of the proposed entry in Annex VI of CLP." (emphasis added)

Further the Proposal claims, that:

(Page 4) "Based on available evidence and information in the registration dossier (e.g. mechanism of carcinogenicity, characterization of the particles), the proposed scope for the Annex VI entry is: 'Titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies'."

This approach confuses and conflates two important and distinct requirements:

- On one hand, the duty of the registrants under the REACH Regulation to submit sufficient information to identify the registered substance in order to assess the risks related to its manufacturing and use based on the data submitted in the dossier (potentially applying read-across); and

- On the other hand, the duty of manufacturers, importers and downstream users under the CLP Regulation (EC) No 1272/2008 to identify the relevant information in order to determine whether the substance – in the form or physical state in which it is placed on the market and is reasonably be expected to be used – entails a physical, health or environmental hazard as set out in Annex I of the CLP Regulation.

The registrants of titanium dioxide have concluded that the data submitted in their Joint Registration dossier were sufficient to determine the safety of the registered substance covered by the agreed Substance Identity Profile (SIP), as manufactured and/or marketed by all the registrants, because these data were not significantly affected by the potential differences between the physicochemical properties of the individual substances tested.

This conclusion was supported by the French Proposal, which – when reviewing the role of physicochemical properties of TiO2 (size, crystalline phase, coating) on carcinogenicity – also concluded that:

(Page 8) "Indeed, TiO2 in all these combination is considered to behave in the same way as other poorly soluble low toxicity particles." Further, it concluded that: (Page 52) "In summary, even if several studies tend to demonstrate that the nano-form is more 'reactive' (biologically active) than the micro-form, none was able to clearly correlate the hazard to specific forms or categories." (emphasis added) And it concluded: (Page 52) "it rather seems that the crystalline form has no significant impact on the carcinogenicity potential of TiO2 since carcinogenic effect was observed with anatase, mix anatase/rutile and rutile forms." (emphasis added)

The French Proposal states that :

(Page 58) "taking this statement [of the registrants] at face value that no combinations of phase, particle size and surface chemistry are considered to impact on properties relevant for the hazard profile and that all combinations of phase, particle size and surface chemistry can therefore be considered equivalent;" and "all forms of TiO2 are susceptible to induce lung tumours, secondary to oxidative stress and chronic inflammation;" "and the classification proposal covers all commercialized titanium dioxide in all phases and

phase combinations; Particles in all sizes/morphologies" The detailed comments from TDMA and TDIC demonstrate that these conclusions are not supported by scientific evidence.
Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Firwood Paints Ltd	BehalfOfAnOrganisation	110
Comment received				
I am writing on behalf of Firwood Paints Ltd Bolton UK who are manufacturers of industrial and decorative paints. Our company has used Titanium Dioxide for over 50 years as our white pigment of choice and have no record of observed ill health effects with our staff as a consequence of this. We have 35 staff of which 15 regularly handle pigments including titanium dioxide. We have no obvious substitute for titanium dioxide and the classification of this pigment as carcinogenic would have serious technical and commercial impacts on our company. We are not aware of other white pigments that could be used as a suitable replacement for titanium dioxide. As should be expected we handle titanium dioxide in a controlled environment with dust extraction equipment and personal protective equipment provided to our staff. We appreciate that good standards of health and safety for our staff are critical for our operations. Our experience in the UK paint industry is that titanium dioxide is handled in a controlled manner with regard to the emission of dusts.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy		BehalfOfAnOrganisation	111
Comment received				
<confidential> has been using TiO2 for more than 50 years; we started using it for synthetic leather (in 1965) and in 1974 we started using it for wallcovering. Until today we used TiO2 for formulation of all our range of product (synthetic leather for bags, for shoes, for clothing, for floorcovering, for wallcovering) and in all our different production divisions, employing more than 700 workers, we never had the evidence of an health problem caused by TiO2. Due to this real and long term experience, I believe that the scientific position provided by TDMA is fully shareable. I want to underline that we are using daily TiO2 and we have been using it for 50 years; our range of product without TiO2 will be strongly effected: the 90% of our wallcovering				

is made using TiO2, 65% of our bags product, 30% of vinyl floorcoverings and 26% of clothing product will be in serious troubles in case we should avoid TiO2 use. <confidential>
Dossier Submitter's Response
See point 2 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	France	European Photocatalysis Federation	BehalfOfAnOrganisation	112
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling | | of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Cyprus	Peletico Ltd	BehalfOfAnOrganisation	113
Comment received				
I represent Peletico Ltd established in the EU Member State of Cyprus and respond on behalf of this company.We are a formulator of paints and we are concerned about the proposal made by France for classifying titanium tioxide as a carcinogen.Our company currently employs fifteen people in the production facility. We have been using this substance for 55 years. As we successfully manage the workplace exposures of dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. We run spirometry tests every year on all production workers with negative results. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixtures and we strongly believe that this would be disproportionate as it would have high economic impact to our market. The health concern is related to the inhalation of dust yet, due to the hazard based approach taken by the European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach, all finished liquid products based on TiO2 would be affected by this new classification. Our business depends on TiO2 and there is no direct replacement for this substance in coatings. If the French proposal is supported it could result in the potential ban of sales of all decorative wall paints and white DIY products to the general public, the introduction of additional measures related to worker safety, product labelling and transportation and legislatively pressure to replace TiO2 in all our products.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	A.I.S.E.	BehalfOfAnOrganisation	114
Comment received				

A.I.S.E. is the International Association for Soaps, Detergents and Maintenance products. Titanium dioxide is safely used in detergents products and the large body of data on TiO2 demonstrates that (1) it does not present a cancer risk for humans via any exposure routes, (2) the classification criteria for carcinogenicity are not met and (3) such classification would require replacement of a well-known safe ingredient for both consumers and the environment, thus not bringing any safety benefits.

A. Toxicological hazard of TiO2 and CLP classification criteria

A.I.S.E. has taken notice of the detailed expert review provided by the Titanium Dioxide Manufacturers Associations (TDMA). A.I.S.E. also concludes that the toxicological data is not supportive of a classification for carcinogenicity based on the summarized items below which are addressed in details in the TDMA response.

(1) Many large epidemiological studies of workers have shown no increase in risk of lung cancer in humans and no evidence indicating a "causal relationship" between exposure to TiO2 and development of lung cancer in humans.

(2) Positive animal data from inhalation carcinogenicity study are only observed in one species at high exposure dose under condition of lung overload where lung clearance mechanisms are overwhelmed, leading to oxidative stress, chronic inflammation and finally tumor formations. The observed effects in rats under lung overload situations are not applicable to humans due to different adverse outcome pathways (mostly driven by different clearance mechanism), as supported by data on non-human primates and coal workers. Furthermore, the fact that similar effects were not observed in non-rat rodents such as mice, hamsters and rabbits suggests it is not a rodent-specific, but in fact a rat-specific effect. Deriving extrapolation for humans based on a species-specific toxicological effect that occurs at very high doses is highly questionable. In addition, validity of data generated under lung overload conditions for carcinogenicity assessment is questionable as OECD guidelines 451/116 recommends that the maximum dose be selected not to "overwhelm normal pulmonary clearance mechanisms".

(3) Consistent with the carcinogenicity studies, the genotoxicity studies demonstrate that TiO2 is not a primary genotoxicant and only under lung overload conditions is there secondary genotoxicity via the induced inflammation and the associated oxidant generation from inflammatory cells. This is considered to be a threshold mechanism of action that would not occur at lower doses of exposure.

All available data in animals and humans indicate that the carcinogenicity observed in rats under lung overload condition is not relevant to humans. This hazard occurs only in rats under specific conditions and does not exert itself in humans. As such, TiO2 should not be classified as a presumed (Cat 1) nor suspected (Cat 2) carcinogens per CLP criteria below.

CLP annex 1 (3.6.1.1) : "substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans".

In addition, the low level use of TiO2 in detergent products leads to TiO2 inhalation

exposure that are many orders of magnitude lower than levels that have been shown not to lead to any carcinogenicity effects in all species, including rats. This further reinforces the weight of evidence suggesting that the level of exposure in consumers cannot be correlated with an actual significant risk of developing lung tumour.

B. Use of TiO2 in A.I.S.E. sector and impact of a CARC 1b classification

TiO2 is present in certain detergent products at levels <1% (with vast majority <0.1%) and it is mostly used as an opacifier or as a stability coating for granular enzymes. Classification of TiO2 as a carcinogen would bring a de facto ban in most detergent applications due to mixture classifications and/or consumer perceptions that that products containing TiO2 are now unsafe for use.

Replacement for enzyme coating is not straightforward and will require significant R&D work from enzyme manufacturers. Enzyme stability is an important aspect of the safe use of enzymes thus TiO2 plays a critical role in insuring consumer safety as it regards respiratory sensitization. There are replacements for the use of TiO2 as an opacifier although they may not have the same well-known safe environmental profile.

TiO2 is a naturally occurring mineral with a long history of safe use across many sectors and with a safe hazard profile both for human and environmental endpoints. Its use in detergent products leads to insignificant consumer exposures via inhalation and replacements will not bring any consumer nor environmental safety benefits.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Netherlands	Rowat bv	BehalfOfAnOrganisation	115
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy		BehalfOfAnOrganisation	116
Comment received				
Titanium Dioxide has been largely used with not known adverse event on humans. Even though epidemiological studies have limitations, the absence of effects should be taken into account ECHA note – A confidential attachment was submitted with the comment above. DECLARATION_(confidential)_2016 TiO2.pdf				

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom		Individual	117
Comment received				
The CLH report acknowledges that human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. Nevertheless, a weak argument is made that lung tumours observed in female rats with grossly overloaded lungs are more relevant to humans than actual human experience because all the epidemiological studies "had methodological limitations; misclassification of exposure could not be ruled out" (page 8). Similar comments can be made about every epidemiological study. However, most of the limitations listed are minor or irrelevant and none seriously limit the ability of the studies to detect an exposure effect, and no reason is given to suggest that misclassification of exposure has undermined the ability of the epidemiological studies to detect an exposure effect. In addition, the CLH report does not mention the second largest cohort study of TiO2 manufacturing workers (over 5000 workers, 133 lung cancer deaths) which also provided no evidence that lung cancer is associated with TiO2 exposure (Ellis et al, 2010; Ellis et al, 2013). Hence, 3 large and well conducted cohort studies (Fryzek et al, 2003; Boffetta et al, 2004; Ellis et al, 2010, 2013) provide little evidence of an increased lung cancer risk among over 24,000 production workers, and no evidence of an exposure-response relationship between TiO2 and mortality from lung cancer. The lack of an exposure effect is supported by two Canadian case-control studies which included over 2000 cases of lung cancer. The dismissal of the strong epidemiological evidence is counter to the CLP regulation (Annex I, section 1.1.1.4), which favours adequate, reliable and representative data on humans from well-powered, robust and high quality studies. It is disappointing that findings from inhalation and intra-tracheal administration of TiO2 to rats in an overload context are given precedence when the relevance of these findings to humans is based on a "hypothesized mode of action requiring a sufficient accumulation of particles to induce inflammation and proliferative lesions" (page 9) in rats, and because "it appears that lung retention and chronic pulmonary inflammation occurring in humans are consistent with the findings in rats" (page 8), even when there is clear evidence that the development of tumours isn't consistent.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	West and Senior Limited (WSL)	BehalfOfAnOrganisation	118
Comment received				
Summary - We disagree with the proposal to re-classify Titanium Dioxide to a class 1B carcinogen				

and question the evidence being used as justification of change in the CLH report. We also support the arguments presented by the Titanium Dioxide Manufacturers Association in challenging this proposal and request early consideration is given to the negative socio economic impact should this re-classification be approved.

Opening comment –

West and Senior Limited (WSL) are a formulator manufacturing pigment and additive systems for supply in to the polymer and associated industry. The company was established in 1952 and has been handling Titanium Dioxide for use as a pigment since that time without health related incident. We disagree with the proposal to re-classify this substance and question the relevance of the limited toxicological evidence submitted versus the many years of high volume, safe use across a multitude of industrial sectors.

The re-classification, if passed, would bring the process of REACH into question with regards to perceived hazard based classification versus actual reality of minimal risk and appropriate risk management.

We support the findings of the Titanium Dioxide Manufacturers Association (TDMA) and the technical questioning submitted in conjunction with Titanium Dioxide Industry Consortium (TDIC).

We kindly ask that ECHA consider the views of those handling this material not only in regard to the initial question on hazard, but also the long term socio economic damage that may result by way of re-classification.

The Technical Importance of Titanium Dioxide -

Titanium Dioxide is used as a pigment in a multitude of plastics articles and whilst first considered as a pigment for white coloured applications, it is also a base pigment for many pale shades covering the entire colour spectrum.

With the highest of certainty, when you consider a plastics article which is white or any pale colour shade, Titanium Dioxide will have been used to enable this colour and it is considered by industry that no known alternative to Titanium Dioxide exists. The use of Titanium Dioxide is not specific to the UK or EU, it is globally recognised as a key substance in the pigmentation and technical performance of plastics articles.

In addition to the base application of colour and colour depth (opacity), titanium dioxide may also impart significant gains to the longevity of an article often working synergistically with other additives to aid long term weathering performance. The ability to protect the polymer from the natural elements and degradation via UV attack allows long term colour stability, but more importantly the retention of physical performance, preventing the polymer becoming brittle, cracked or easily damaged.

WSL supply of Titanium Dioxide preparations to the polymer industry can be found across numerous articles and within a wide variety of demanding environments for example –

• Construction – window profiles, thermal cladding, rainwater and drainage, wood replacement articles, roof, wall, ceiling and flooring coatings, heat reflective panels, water tanks
• Marine – motor boats, yachts, small craft, corrosion resistant coatings, off-shore wind turbines

• Transport – automotive panels, automotive protective film, caravans, motorhomes, trucks, trains, tarpaulins, road markings • Home & Leisure – flooring, wallcovering, furniture, clothing, sporting goods, playground and sports surfaces • Medical – plasters, wound dressings, equipment housings • Advertising – graphic films, signage The use and technical importance of Titanium Dioxide should not be underestimated and a classification to carcinogen status would have unparalleled impact downstream and in turn with consumer confidence without positive gain towards actual risk which is believed minimal based on long term factual safe use. Safe Use and Handling - Titanium Dioxide is supplied in its raw form as a powder. Whilst WSL as a company then blends this substance with other components or indeed prepares dust free liquid phase dispersions, we acknowledge manual handling exists and through our manufacturing plant we handle several hundred tonnes per annum including multiple grades and supply routes. When the long term history of our company is considered, it is clearly apparent that we have used, and I stress again without incident, several tens of thousands of tonnes. Our staff are well versed in the handling of powders and our equipment is supported by means of dust containment, extraction and collection. Dust masks are provided when handling titanium dioxide but this has always been standard practice when handling fine particulate powders which may become airborne. This is not due to any specific concern relating to Titanium Dioxide as an individual substance. Our workforce handling this material have in many cases been employed as long term employees with decades as opposed to years of experience and none have expressed specific concern associated to Titanium Dioxide. We consider our company as a responsible employer and supplier of goods and have supported the implementation of REACH and the principles towards a safer working and personal environment. We have supported a positive approach at a multitude of international levels of Authority but sincerely question the validity of proposal based predominately upon a limited series of questionable animal laboratory testing versus the practical evidence of long term, high volume safe industrial use across a wide range of application, handling practice and geographical location. We envisage that we are not alone in these thoughts and are aware that the proposal has already caused great concern and confusion amongst industry members reliant upon the safe, technical gains of this vital substance. Closing Comment – West and Senior Limited, as a concerned party and industrial user of Titanium Dioxide, sincerely ask that ECHA reject the proposal to re-classify Titanium Dioxide to a category 1B Carcinogen (H350i). ECHA note – A non confidential attachment was submitted with the comment above. Titanium Dioxide Response to Public Consultation WSL.pdf
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy		Individual	119
Comment received				
I am <confidential>. I am the occupational Doctor of the Company Salchi Metalcoat, responsible of the medical survaillance since 1978. I can declare that in all these years I have never found a correlation between the use of titanium dioxide and upper respiratory ways and/or lung diseases, including cancer. The medical survaillance is performed both by instrumental and clinical controls. Salchi Metalcoat S.r.l produces varnishes containing big amounts of titanium dioxide, so the workers can be considered exposed.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	PlasticsEurope Deutschland e.V.	BehalfOfAnOrganisation	120
Comment received				
Titanium dioxide has been used safely for many decades. No increased incidence of lung cancer has been observed. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report: "Human data do not suggest an association between occupational exposure to TiO2 and risk of cancer […]" [CLH Report, page 8]. The classification proposal in the CLH report is based essentially on studies in rats exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and the ECETOC Report unanimously observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons. Therefore, a classification is neither justified nor appropriate from the toxicological perspective. Because of its outstanding properties, titanium dioxide is an all-rounder raw material in almost all sectors of industry. This substance is widely used, mainly as white pigment and particularly in paints, coatings, plastics, textiles, foods and feedstuffs, in paper production as well as in pharmaceutical and cosmetic products. A classification as "potentially carcinogenic to humans" would have considerable negative impacts on entire value chains.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Switzerland	Novartis	BehalfOfAnOrganisation	121
Comment received				
There is no known risk for carcinogenicity of TiO2 with dermal or oral exposure. For inhalation exposure, there is evidence for carcinogenicity in rats only at very high doses leading to lung overload. Lung overload is considered to be a species-specific mechanism in rats. Large epidemiologic studies in workers handling different types of TiO2 did not show any relationship between workplace exposure and cancer incidence. In summary, we consider assigning a hazard classification of category 1B ("presumed to have carcinogenic potential for humans") / H350i 'may cause cancer by inhalation' for TiO2 not to be applicable. The proposed change in classification and labelling would not contribute to the protection of workers exposed to all modifications and particle sizes of TiO2. ECHA note – A non confidential attachment was submitted with the comment above. NVS final.pdf				
Dossier Submitter's Response				
See points 1 ,2 and 4 of the attachment to the RCOM. For specific point in the attachment linked to skin and oral exposure, no carcinogenic potential is expected for titanium dioxide as assessed in the CLH report.				
RAC's response				
Noted. RAC concluded that the TiO2 profile of lung carcinogenicity is specifically linked to the inhalation route. Available data with oral and dermal exposure did not result in TiO2 carcinogenicity.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	IMA-Europe	BehalfOfAnOrganisation	122
Comment received				
IMA-Europe is an umbrella organisation which brings together a number of European associations specific to individual minerals: Calcium Carbonate (GCC/PCC), Dolomite, Andalusite, Bentonite, Borates, Diatomite, Feldspar, Kaolin, Lime, Mica, Plastic Clays, Sepiolite, Silica, Talc and Vermiculite. Together, IMA-Europe's associations represent over 500 companies in 28 countries. The yearly production of industrial minerals in the EU is about 180 million tons. While member companies of IMA-Europe are not producing titanium dioxide (TiO2), the naturally occurring industrial minerals they produce may contain TiO2 up to 3%. Therefore, If titanium dioxide is given a harmonized classification as a carcinogen 1B by inhalation (H350i), many industrial minerals would have to be classified due to the presence of this natural impurity above 0.1%. This would represent an annual volume of about 20 million tons of natural raw material to be classified and, therefore, subject to market restrictions. Furthermore, the ore containing those raw materials may also be found as a carcinogen and then we are talking probably hundreds of million tonnes of materials being called a carcinogen. At the minimum a reasonable impact study should be necessary. Consequently, a harmonized classification of TiO2 as a carcinogen 1B can only be supported if there are unequivocal data supporting the classification. According to our assessment (see details below), this is not the case in the CLH dossier on TiO2 as presented by France. Substance identity The CLH dossier covers titanium dioxide (TiO2) in all phases and phase combinations				

including anatase and rutile polymorphs. We see discrepancies between the scope of the CLH dossier and the REACH registration dossier for titanium dioxide which also cover titanium tetrahydroxide [Ti(OH)4] and titanium dihydroxide oxide [Ti(OH)2O]. More so, the CLH dossier specifies that the degree of purity of TiO2 is above 87%. Thus, what about TiO2 with a degree of purity below 87% (for instance, where part of the titanium is substituted in the crystal structure by another element such as aluminium, magnesium or manganese) and present as an impurity in natural industrial minerals?
The animal studies supporting the classification have been conducted on TiO2 with a purity level of 99.5% or higher produced synthetically using chemical processes. Are there any scientific evidence to extrapolate these studies to lower purity grades of TiO2 or on those present in natural minerals as trace level impurities The CLH dossier does not address this aspect.

Particles size
The CLH dossier proposes to cover "particles in all sizes" while the animal studies have been conducted on either nanomaterials or ultrafine powders (about 1.6 □m). While TiO2 is placed on the market with a fine granulometry, industrial minerals containing TiO2 as an impurity, are an order of magnitude coarser (5 – 100 microns). Therefore, it would be appropriate to specify an upper limit of particles' size for which the proposed classification would apply.
Procedure & timing
The CLH dossier highlights a number of datagaps to allow an in-depth assessment of the potential toxicity of different forms, morphologies or particle sizes. As a consequence, France seems to adopt an inappropriate "one size fits all" solution. Since ECHA is finalizing a dossier evaluation for TiO2 and France itself has notified its intention to conduct a substance evaluation on TiO2 in 2017, no regulation should be proposed until these studies are complete. On this matter, in our opinion, the logical approach would beas follows: compilation of all the data necessary for a robust assessment and, then, drawing up conclusions on whether or not to classify the concerned substance. Hence we firmly believe that operating the other way around is not the right approach.
Furthermore, if a regulation is to be proposed, it is essential to establish traceable mineral standards as well as methodogy for the analysis of the material.

Conclusion on the carcinogenic effects of TiO2
The conclusion of the CLH dossier is based on two studies presented as "of acceptable quality". However, one of them, Lee et al (1995) study, does not meet the OECD Guidelines requirements because of the following arguments:
• The ECHA guidance on the Application of the CLP criteria (Version 4.1, June 2015) reads: "Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard" (section 3.6.2.3.2., p.379-380).
• The OECD Guideline 451 for the conduct of carcinogenicity studies, in conjunction with the relevant OECD guidance document 116, highlights on various occasions that inhalation concentrations overwhelming physiological mechanisms are in exceedance of the maximum tolerated dose (MTD).
Therefore, the high doses (50 mg/m³ and 250 mg/m³) in the studies of Lee et al (1995) should be discarded for the hazard assessment and, consequently, only one study meeting the OECD guideline requirements remains. From this observation and if the Guidelines are strictly followed, it appears that there are not enough reliable data to reach a conclusion on classification of TiO2.
Weight of evidence and expert judgment
Due to uncertainties related to the animal studies presented in the CLH dossier (see

points above) and the clear absence of health effects in humans (from epidemological studies), IMA-Europe would request ECHA to apply the weight of evidence and expert judgement to the hazard assessment of TiO2.
From our assessment, TiO2 does not meet the criteria for classification as a carcinogen category 1B.

Dossier Submitter's Response

See points 1, 2 and 4 of the attachment to the RCOM.

Regarding comment on purity: 87% purity reported in the CLH report is issued from the registration dossier. We aknowledge that positive carcinogenicity studies were performed with a 99% pure TiO_2 (where data on purity were available). However, entries in Annex VI to the CLP Regulation refer to substances irrespective of their purity (or impurities, if they do not influence the classification).

RAC's response

RAC concurs with the response of the Dossier Submitter that entries in Annex VI to the CLP Regulation refer to substances irrespective of their purity (or impurities, if they do not influence the classification).

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	ALBIS Plastic GMBH	BehalfOfAnOrganisation	123

Comment received

We use TIO2 in amounts of 30 tons per year compounding plastics for different industries. The suggested classification of the substance as Carc. 1B – H350i would lead to major impacts in these industries. In order to improve work safety during manufacturing it would be more helpful to introduce EU-binding occupational exposure limits (OELs) for all dust particles, like several countries have already done on a national level.

Dossier Submitter's Response

See points 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		BehalfOfAnOrganisation	124

Comment received

We are a manufacturer of pigments using titanium dioxide as raw material for our products. On behalf of my company I would like to express my grave concern about the proposal made by France for classifying titanium dioxide as a carcinogen.
We have been using titanium dioxide in powder form for many years by successfully managing the workplace exposures of dust through permanent measures eg. housings or controlled air exchange. This is also necessary to comply with the general dust limit which is enforced in Germany like in many other European countries
Based on our constant biomonitoring we are not aware of any increases of cancer rates of our workers relative to the general population. We are not aware of any epidemological valent study showing a link between the exposition to titanium dioxide to cancer in humans. The classification proposal in the CLH report is based essentially on studies in rats, exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload"-effects.
All relevant guidance documents by ECHA, OECD and ECETOC-Report unanimously observe that the results from "lung overload" studies in rats should not be transferred to

humans for several reasons. Therefore, a classification is neither justified nor appropriate from the toxicological perspective. For justification purposes, we refer to CLP regulation Annex I, 3.9.2.8.1.(e): "substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification." The respective guidance document to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Ver 4.1 June 2015 - explicitly states that overload studies are still part of the scientific discussion. As long as the French MSCA provides no justification why - in this case - the current guidance opinion does not apply, the evidential weight of the cited "lung overload" studies is weak. For identifying carcinogens, CLP (as well as GHS) requires intrinsic data, which establish a link between the substance and cancer. With regard to this provisions and the dossier is self contradictory: „All possible crystal modifications, morphologies and surface chemistries in all possible combi-nations of TiO2 are expected to be biopersistent and of poor solubility, and therefore covered by this CLH dossier. Indeed TiO2 in all these combination is considered to behave in the same way as other poorly soluble low toxicity particles." (CLH report, p. 8). So the property is not intrinsic. The proposed classification would also affect all chemical mixtures containing titanium dioxide and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our pigment preparations must face a direct or indirect loss in sales either through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards .
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Kestrel Building Products	BehalfOfAnOrganisation	125
Comment received				
Kestrel Building Products has used Titanium Dioxide since 1986 with no safety issues raised and thousands of tonnes processed. ECHA note – A confidential attachment was submitted with the comment above. Kestrel Building Products - Classification Proposal for Titanium Dioxide.docx				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Netherlands	AkzoNobel	BehalfOfAnOrganisation	126
Comment received				

AkzoNobel manufactures liquid paints and coatings globally for professional and consumer uses. TiO2 is an essential ingredient in these products, providing colour and opacity to paint films, for which there are no alternatives available. Having reviewed the scientific data available and the ANSES report we consider the following key points relevant to the review:

• The TiO2-induced lung tumours in rats are considered to be due to a secondary genotoxicity mode of action resulting from inflammation caused by particle overload in the lung. This is acknowledged in the CLH dossier. These effects of TiO2 are not seen in other animal models such as the mouse and hamster with the conclusion that they are rat specific. The effect has not been reported in humans. This lung overload phenomenon is not specific to TiO2 as it is seen with other poorly soluble dusts in rats – and not in mice, hamsters, monkeys and humans - and is an effect that has been well documented in the scientific literature. Therefore, the relevance of this rat specific effect is of limited value for classification and labelling purposes and any subsequent risk assessment.

• The lack of substantiated evidence for a direct genotoxic effect. It is noted that no classification proposal has been made for germ cell mutagenicity as no clear conclusions can be drawn from the current extensive dataset.

• A number of reviews of human occupational exposure to TiO2 and other poorly soluble dusts have not provided conclusive evidence of an increased risk of cancer in humans including the IARC review of TiO2 in 2006. Our own internal health monitoring programmes have not identified any adverse health effects related to the inhalation of poorly soluble dusts such as TiO2 in workers in our paint manufacturing sites.

For the reasons stated above we conclude that the weight of evidence does not support classification as carcinogenic 1B by inhalation and fully support the position of the Titanium Dioxide Manufacturers Association (TDMA) that no hazard classification is required for TiO2.

Furthermore, consumer paint products are placed on the market in liquid format so the inhalation exposure to TiO2 dust is not relevant when assessing their safe use by consumers. However, the proposed classification would lead to an automatic restriction on use in consumer products according to REACH Annex XVII entry 28 without any benefits for public health and the environment, resulting in the unnecessary and unwarranted removal of paint products from the consumer market.

Any remaining concerns around occupational exposure of poorly soluble dusts to factory workers should be managed/regulated by an appropriate occupational exposure limit.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	France	FEPA	BehalfOfAnOrganisation	127
Comment received				
ECHA note - Only a non confidential attachment was submitted. FEPA_Answer to the public consultation TiO2 - July 2016.pdf				

Dossier Submitter's Response
See points 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Swish Building Products	BehalfOfAnOrganisation	128
Comment received				
Swish Building Products has used titanium dioxide sine 1976 with no safety issues raised and thousands of tonnes processed. ECHA note – A confidential attachment was submitted with the comment above. Swish Building Products Oppose the French Classification Proposal for Titanium Dioxide.docx				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Bayer AG	BehalfOfAnOrganisation	129
Comment received				
Titanium dioxide is an important constituent of a wide range of cosmetic products like sunscreens, skin care products and tooth pastes. Although no dust exposure for end consumers can be expected, a classification of Titanium dioxide as carcinogenic by inhalation H350i would ban its use in a wide range of cosmetic products intended for consumer use due to regulation (EC) No 1223/2009 on cosmetic products. In this context the CMR classification does not improve the intended protection of health and environment but it could cause a lot of problematic substitutions effects in highly regulated areas (e.g. cosmetics, food and feed additives). Titanium dioxide has been used safely for many decades. From the toxicological perspective no increased incidence of lung cancer has been observed. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report. The classification proposal in the CLH report is based essentially on studies in rats exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload" effects. As regards inhalation toxicity through insoluble, inert particles, the rat is a particular sensitive species compared with all other studied species: Up to now, evidence of tumours in the respiratory tract has been only found in rats after exposure with insoluble, inert particles. Other species – like mouse or hamster – did not develop lung tumours at comparable exposure. Tumour formation in rats is essentially due to particle-induced inflammatory reactions, cell proliferations, secondary genotoxicity through reactive oxygen species and resulting hyperplasia. The above-described effects occur particularly in the overload range where particle clearance (clearance/elimination) by alveolar macro¬phages is massively				

disturbed. These effects have not been found at all or not to a comparable degree in other species at comparable dose and particle load.
The exposure pathway in which titanium dioxide shows a carcinogenic effect exclusively in animal testing is solely exposure by inhalation to titanium dioxide dusts. The effect is not substance-specific and - like mentioned before - based primarily on particle-caused inflammatory processes in the lungs that can lead to tumour formation. Where titanium dioxide comes e.g. in the form of a suspension, the particle-caused inflammatory effects do not come about. Exposure by inhalation to titanium dioxide dusts can be expected primarily at the workplace.
In Germany, dust exposure at the workplace is already covered by the general and very strict dust limit value (allgemeiner Staubgrenzwert/ASGW). Comparable values in other European countries can be taken from the GESTIS database for international limit values under "Dust, respirable".
A new health-based dust limit value of 1.25 mg/m3 for the respirable fraction and 10 mg/m3 for the inhalable fraction was laid down in 2014 and published in the technical rules for hazardous substances TRGS 900. For health-based workplace limit values, it is taken that no hazard to workers' health needs to be assumed if workplace exposure is below the workplace limit value. The general dust limit value applies for poorly soluble or insoluble dusts which are not regulated elsewhere. The TRGS 900 comprises a non-exhaustive list of examples of substances for which the general dust limit value (ASGW) is applicable. This list includes titanium dioxide (TRGS 900, chapter 2.5, entry 12). Consequently, titanium dioxide falls under the scope of the general dust limit value. Furthermore, the requirements to employers for activities with mineral dusts are concretized in the technical rules for hazardous substances TRGS 559 "Mineral dust". Here, inter alia, provisions are laid down for how to carry out the risk assessment for exposure to mineral dusts, what protection measures to derive and how to proceed in prevention within occupational medicine.
Thus, in Germany a high level of protection is achieved for workers in activities with titanium dioxide dusts.
The European directives on the protection of the health and safety of workers from the risks related to chemical agents at work (Directive 98/24/EC) and from the risks related to exposure to carcinogens or mutagens at work (Directive 2004/37/EC) do not yet have any comparable equivalent to the general dust limit value (ASGW). However, Directive 2004/37/EU (carcinogens and mutagens directive) includes rules for the exposure to hardwood dusts. This could be seen as an equivalent.
Transposition into national law of the binding occupational exposure limit value (BOEL), as laid down in the carcinogens and mutagens directive, is mandatory for the EU Member States. Furthermore, the measures for the protection from exposure to carcinogens, as prescribed in Directive 2004/37/EC, need to be taken. This includes, inter alia, examining for potential replacements of substances or processes, minimising exposure where replacing is not feasible, instruction of workers, use of suitable protection measures etc.
Conclusion:
Classification of work exposing workers to titanium dioxide dusts in Annex I to the cancer directive and laying down a binding occupational exposure limit value (BOEL) in Annex III to the directive are also thinkable for harmonising the protection of workers from exposure to titanium dioxide dusts. This procedure should be given preference over a CMR classification of titanium dioxide that would ban titan dioxide as established ingredients in a very wide range of cosmetic products for end consumers. The substitution of titan dioxide would cause an inappropriate and very high burden on the affected industry without any socio economic benefit and no further contribution to the protection of health and environment.

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria	Gesellschaft Österreichischer Chemiker / Austrian Chemical Society	BehalfOfAnOrganisation	130

Comment received

ECHA has opened the public consultation concerning titanium dioxide according to the resume submitted by ANSES. The Austrian Chemical Society (GÖCH) invited the members of the corresponding working groups to respond to the investigative questionnaire and provide their opinions on the suspicion of malign degeneration by impact of particulate TiO2 on living cells. Our statement is the result of consulting the broad expertise of our members and is free of influence of any political, industrial or other interests. To make visible the direct connections to the presented ANSES-document we integrate here the original text made visible by apostrophes.

The responses we got qualified the kind of reaction as typical for living cells confronted with particles of foreign matter without specificity to a chemically defined compound.
Cit.: "The proposed mechanism is already described for other substances such as aluminium oxide, insoluble nickel salts and iron oxides, acting as poorly soluble low toxicity particles, which elicit lung tumors in rats following prolonged exposure at sufficiently high concentrations."
Every contact of a certain amount of such a material with biological systems leads to an inflammatory reaction with a certain probability to being precancerous.
Reflecting the experience of members specializing in toxicology within GÖCH, the cause-effect-relation of such investigations as shown in the presented report is to categorize as physical-particle-oriented and not chemical-compound-based. Therefore, specific restrictions under the label TiO2 will not be justified, even if the text suggests them with regard to the nano-form.
Such a warning seems only justified if more evidence based data of occupational health & safety associations, evaluated by competent experts, verify a specifically substance connected hazard and indicate a concrete probability of a risk generated by perpetuated exposure. According to the present knowledge of GÖCH, this is not the case. As an example, already J. Ferin and M. L. Feldstein (Environ. Res. 16 (1978) 342-352 contributed data to this question.
Cit,: "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable.

Although it was initially foreseen to propose a harmonized classification for mutagenicity, this hazard category has been put aside from the proposal because the existing data show too many discrepancies that cannot be explained with the current state of the science. Indeed, the FR-MSCA was not able to identify specific physicochemical parameters justifying the discrepancies along the mutagenic results and whether the differences reported in the results could be due to different study protocols having been employed. For this endpoint, further data are necessary to consolidate the existing data and see if specific forms are leading to more severe toxicity than others. Genotoxicity dataset on TiO2 is therefore only presented as supporting data for carcinogenicity endpoint, and summarized in Annex I"
Therefore, we recommend starting clear and concise prospective investigations. Only

these will create valid data to support a decision and make correct advices possible, independently of the present view focused on a single, but multiform material. At the same time, the dose-dependent criteria have to be taken into account.

Additionally we want to mention that the precautionary principle is not applicable because the pre-condition of an assumable hazard for human beings is lacking.
Cit.: "Inhalation route - Human data: Methodological limitations were noted for all studies. In addition data on primary particle size or size distribution of the TiO2 particles were lacking. In this context, epidemiological data are considered inadequate

No increase of lung tumors was reported in two other inhalation studies performed in rats with TiO2, type Bayertitan T, 99.5 % rutile (Muhle, 1989, 1991, 1995,) or with TiO2 "standard size" with 99.9% < 0.5 µm (Thyssen, 1978). However, the Muhle study was performed at a concentration lower than those associated with lung tumor in the two above studies. The Thyssen study was only performed for 12 weeks, a duration not sufficient to adequately assess any carcinogenicity potential."

Taking into consideration the widespread use of TiO2 and being fully aware of its responsibility, the Austrian Chemical Society does not recommend to classify TiO2 as carcinogenetic material based on the available data.

Dossier Submitter's Response
See points 2 and 3 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		BehalfOfAnOrganisation	131

Comment received

Of course, consumer protection is of top priority and the safe use of a substance must be ensured also under working conditions. Therefore, already today, TiO2 is strictly regulated due to occupational safety requirements (e.g. general threshold limit value for dust and risk-management measurements), which ensure safe handling of the substance.

Also in other areas like pharmacy, as well as cosmetics and food industry the safe use of TiO2 is guaranteed by an extensive risk assessment and – if necessary – appropriate instructions of use. The inhalative absorption of TiO2 by end-users is generally minimal, because TiO2 is usually embedded in a product matrix which significantly reduces or even prevents inhalative exposure.
As part of the legally required safety assessment the safe use of any raw material for cosmetic use must be ensured prior to use. Accordingly, each ingredient, its specific level of use as well as exposure through the cosmetic product (amount and type of application) and special target groups (e.g. pregnant women and children) are considered. In contrast to the CLP-Regulation, a risk-based approach rather than a hazard based approach is used.
In the same way TiO2 is evaluated as part of a cosmetic powder product. Among others, a potential risk due to an inhalative intake of powder particles is taken into account. In a first step the respirable fraction of the product is determined by appropriate analytical methods. Afterwards, the results are related to the amount of application, the volume of distribution, the human respiration rate and existing dust limits. The safe usage of the product including all its ingredients (e.g. TiO2) must be proven accordingly.

The reclassification of TiO2 would have major impact on producers of cosmetic products. Not only the use of the reliable, safe and important ingredient TiO2 would be impossible or at least significantly limited, also the public and the consumers would be considerably concerned and irritated by this unexpected classification.
Dossier Submitter's Response
See points 1, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria	Borealis	BehalfOfAnOrganisation	132
Comment received				
Borealis supports and agrees with the TDMA/TDIC position of no classification of titanium dioxide (TiO2). In decades of using TiO2 in Borealis, no observation was made that would point towards a connection between TiO2 exposure and cancer in humans which is also confirmed by the CLH report on page 8. In Borealis we use up to 1000 tonnes per year of TiO2. The vast majority is used as pigment for polyolefins going into automotive, appliances, and pipe applications. Since we mainly use it in the form of pelletised masterbatches the risk of exposure to TiO2 dust in our plants is very limited. Once embedded in the polymer matrix no respiratory exposure is possible any more further down the supply chain. There is no commercially available alternative for TiO2 available for the mentioned applications due to its superior stability towards moisture and UV light. If we would have to stop using TiO2 for above described applications as consequence of the proposed classification as carcinogen category 1B, the financial impact on Borealis and its customers, a lot of which are SMEs, would be very high. We foresee an increase in price of consumer goods that consist of coloured plastic parts and/or a move of related industry sectors outside the European Union leading to loss of employment in Europe.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	SunChemical Ltd	BehalfOfAnOrganisation	133
Comment received				
The proposal to classify Titanium Dioxide as Carcinogenic 1Bi is neither justified nor appropriate based on the dossier submission. The proposal has presented no new new evidence ; the lung overload phenomenon in rats is widely accepted to be a species specific phenomenon and that this species phenomenon should not be transferrable to humans. We refer to CLP Regulation Annex I, 3.9.2.8.1 (e) where "substance-induced species-specific mechanisms of toxicity i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification. Within the Printing Ink industry Titanium Dioxide has presented safe use for many decades with no indications of issues from epidemiological studies or use in practice. A				

classification as Carcinogenic would not enhance the protection of workers health. It would, however, have disproportionately adverse consequences in all Printing Inks blends where Titanium Dioxide is a contributing colouring component. In conclusion the CLH proposal is inappropriate and no classification as hazardous should be made.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Clariant Produkte (DE) GmbH	BehalfOfAnOrganisation	134
Comment received				
Comments on the proposed harmonized C&L of titanium dioxide ECHA note – A non confidential attachment was submitted with the comment above. Clariant_Opinion on Classification Proposal for TiO2_14072016.pdf				
Dossier Submitter's Response				
See points 2 and 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria		BehalfOfAnOrganisation	135
Comment received				
As manufacturer for paints , plasters and special coatings we use TIO2 in a range of more than 30 years. Till now no case of health attack caused by TIO2 to our customer are observed. TIO2 is tightly bound in our products and therefore not exposed in inhalation modification. TIO2 is the unique component in our products to achieve properties of white color and protection against color – instability. TIO2 is not to substitute by other raw materials. In case the proposed classification will come into effect it will result in extremely disastrous commercial turbulences. How to handle TIO2 in our production plant is regulated by the appropriate safety dada sheets and controlled by external safety commissioner.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	CIRFS Man-made Fibres Organisation	BehalfOfAnOrganisation	136
Comment received				
Man-made fibre producers are users of titanium dioxide (as) imbedded in fibres for delustering, whitening and UV resilience of the fibres within the range of 0.1-1.5 % (level				

depending on the lustre required by end users). The substance is used safely and these fibres have been sold to the end use market for many decades.
The manufacturers' recommendation is always reliable and obeyed upon during plant exposure, in the handling and processing of the substance.
The substance which is chemically inert (does not react in processing) is excellent in light fastness and weathering stability, particle size for micro fibre production size and cost efficiency.
If the classification of the substance causes the use to be stopped in fibre production, the impact on the man-made fibre industry will be very high since there is no known commercial, cost competitive and available alternative for the application purpose.
We leave the specific section comments on carcinogenicity, mutagenicity, respiratory sensitisation and reproductive toxicity to the producers and related organisations.

ECHA note – A non confidential attachment was submitted with the comment above.
CIRFS response to ECHA Consultation on Titanium Dioxide.pdf

Dossier Submitter's Response

See point 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	MedPharmPlast Europe	BehalfOfAnOrganisation	137

Comment received

See MedPharmPlast Europe Position Paper

ECHA note – A non confidential attachment was submitted with the comment above.
MPPE Position Paper - Classification of TiO2.pdf

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Poland	Federation of Polish Paints and Adhesives Industry	BehalfOfAnOrganisation	138

Comment received

The experience of Polish producers in the past 40 years have not confirmed the TI02 impact on health of employees. There were no such cases in the past (during the week-quality infrastructure), and thus it is more difficult to suspect in the future, where old factories have been converted into modern production facilities. More and more automated dispensing systems cause minimal human contact with the raw materials.
In addition, we see the following arguments against the classification of a group Ti02 1B:
• raised safety rules - Use of effective ventilation and other safety measures, including rules on the use of materials and raw materials.
• In case of contact with the consumer paint dealing with liquid product – no dust. With the current composition of the paint thanks to the large amount of binder risk of inhaling dust does not exist
• consequences for companies: lack of alternatives, widely used titanium white. Such a

huge change in the paint industry may impact more on smaller companies that do not adapt to such a huge changes, and consequently disappear from the market Refer to aspect 4, detailed in page 1
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy	Cromology	BehalfOfAnOrganisation	139
Comment received				
Cromology produces paints for over 250 years and is today a world player in the decorative paint sector. The Group ranks in second place in France and is the market leader in Southern Europe (Italy, Spain and Portugal) with 13 production facilities and 4,000 employees. Cromology is very concerned about the proposal made by France to classify titanium dioxide as a carcinogen. Titanium dioxide is an essential raw material in formulation of our paints (mixtures). It provides key properties to our products, such as whiteness, opacity, brightness, protection from UV light, stability and durability. The proposed classification, as well as having an impact on the management of workplace exposure in our factories, would have a very strong impact on the classification of our products. The final result of this new classification will be the ban on selling all decorative wall paints and white DIY products to the general public. The proposed classification is contradictory with our daily experience of use of this raw material. We use more than many thousands tons per year but we don't have any evidence of cases of cancer in our workforce caused by inhalation of TiO2 during the manufacture of paints and coatings, over the last 30 years. We think that there is a general question in handling all types of powders to prevent from dust exposure, rather than specifically related to TiO2, what conduct us to put in place, in our facilities, the appropriate risk management measures. However, the question linked with exposure to dust is not an issue when used in a liquid matrix such as paints. This Question is of very high priority for our industry as Tio2 is an essential Raw Material.				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy	Iris Green s.r.l.	BehalfOfAnOrganisation	140
Comment received				
We produce mixtures for different fields of application (paints, toys, plastic materials) containing more than 1% of titanium dioxide. According to the proposed classification (H350i) and the concentration in our mixtures, it means that all our products will be classified H350i with a huge impact not only for our business but also for the whole paint, toys and plastic markets. I take this opportunity to ask if the classification H350i (inhalation) still remain even if the powder will be dispersed in an aqueous medium and the final state is liquid and not powder. Thanks for clarification				

Dossier Submitter's Response
See points 1 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	KEIMFARBEN GmbH	BehalfOfAnOrganisation	141
Comment received				
I represent the company KEIMFARBEN with headquarters in Germany and subsidiaries in Austria, Belgium, Czech Republic, Denmark, France, Great Britain, Hungary, Italy, Nederland, Poland, Spain, Sweden and Switzerland and I respond on behalf of that company. We are a formulator of silicate wall paints and renders and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs about 500 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	PlasticsEurope AISBL	BehalfOfAnOrganisation	142
Comment received				
PlasticsEurope wishes to point out the wide use of Titanium Dioxide in the polymer industry and the very significant impact on industrial and consumer products that could occur if the use of Titanium Dioxide were to be restricted. PlasticsEurope fully respects the scientific analysis that leads to hazard classification of substances, but requests that the most thorough possible processes are applied to the assessment in the case of Titanium Dioxide in view of its importance of to our industry.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		Individual	143
Comment received				
Since our company ARGUS Additive Plastics GmbH has been in business we are using a lot of TiO2 and we do not observe any negative health effects concerning the possible inhalation of TiO2 powder during processing				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Greece		BehalfOfAnOrganisation	144
Comment received				
We are masterbatch producers in Greece. TiO2 has been used in our company since 1980 without any problems. We apply ventilation systems and our employees in the mixing sector use suitable disposable masks to avoid exposure to TiO2 powder. If the classification of TiO2 as a carcinogen 1B by inhalation (H350i) is agreed upon we are going to face serious problems since there is no suitable substitute. Besides TiO2 classification might lead to similar actions regarding the use of other powders as ATH, calcium carbonate, talc etc. The effect on many industries will be severe. It is worth to underline the conclusion of the resent CLH report (page 66) "Available human data on the effects of titanium dioxide are rare, exposure was generally indirect, with possible co-exposure to other nanoparticles. The studies were not conclusive and had weaknesses. Human data are therefore insufficient to classify titanium dioxide as Carc. 1A."				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		BehalfOfAnOrganisation	145
Comment received				
Titandioxid is used as a pigment in our rubber mixtures. Significant amounts above are used within West. In case the classification as a carcinogen 1B by inhalation is agreed upon we are facing serious problems, as there are no substitutes available. In effect we would lose a significant portion of our business and this might ultimately also lead to a loss of jobs. In addition, our customers would not be able to package pharmaceutical drugs anymore. This could lead to a major impact on millions of patients, which cannot be treated anymore until a recertification of the primary packaging has taken place.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Profine Group	BehalfOfAnOrganisation	146
Comment received				
Our Company is using more than 10.000 tons of TiO2 per year. Until now, no health issues related to TiO2 have been reported in our Company. A classification of TiO2 as carcinogenic 1B would lead to a classification of the PVC compound as well. We expact negative Impacts on:				

- Image for PVC window and sheet products in the public will be damaged. - cost for additional safety measurements will harm the competitiveness of window products on the market
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Turkey	Aksa Akrilik Kimya Sanayi A.S.	BehalfOfAnOrganisation	147
Comment received				
Titanium dioxide is used as an additive in both dull and semi-dull acrylic fiber for over forty years. We didn't observe any case of cancer caused by Titanium dioxide				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	BASF Coatings GmbH	BehalfOfAnOrganisation	148
Comment received				
BASF Coatings, the international Coatings Division of the BASF Group, produces and markets automotive OEM coatings, automotive refinishes and industrial coatings as well as decorative paints. We are a downstream user of Titanium dioxide, which is a very important component of our products. Titanium dioxide is used in several paint production sites in Europe. As for other solids, workers inhalative exposure to dust is controlled and risk reductions measures are in place. The general dust limit values (TRGS 900 in Germany, similar limit values in other countries) are observed. Although Titanium dioxide has been used for many decades, no increased worker's incidence of lung cancer has been observed. Exposure of humans to Titanium dioxide dust is not an issue for the users of liquid paints and coatings. Because of its outstanding properties, Titanium dioxide is widely used as a white pigment and in our paints and coatings. Suitable alternatives are not available. Other white pigments do not meet the technical performance of Titanium dioxide, are hazardous and less cost efficient. Substitution of Titanium dioxide by such alternatives would lead to paints and coatings of inferior quality with respect to stability, brightness, opacity, abration resistance and other properties. This would not be acceptable for our customers.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria	Synthesa Chemie Ges. m. b. H.	BehalfOfAnOrganisation	149
Comment received				
Our company produces interior and exterior wall paints, opaque lacquers, plasters, wood varnishes etc. since 1946 and therefore Titanium dioxide is an essential ingredient as a white pigment. Up to 2.000 tons per year are currently used as raw material. There is no adequate substitute and the loss of this pigment would cause an enormous economic loss. We are sure there is no danger to health outgoing from this material because in all these years no damages to health was observed neither at our employees nor at our customers.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Switzerland		BehalfOfAnOrganisation	150
Comment received				
TiO2 is used by our company in the formulation of security inks, which are commercialized to professional printers only. It is used on industrial sites, with appropriate protection measures. Dust measurements are carried out at workplaces. No health effect related to the use of the substance has been observed to date. We support and agree with the TDMA/TDIC position of no classification of TiO2.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Siegwerk	BehalfOfAnOrganisation	151
Comment received				
I represent the company Siegwerk with headquarters in Germany and subsidiaries in 10 other EU member states and I respond on behalf of that company. Siegwerk is one of the leading packing ink manufacturers worldwide. Our company currently employs around 1700 people in the European Union. We are highly concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. With regard to the toxicological assessment and subsequent conclusions we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy. Titanium dioxide is of even more importance for the packing printing segment since white backup layers are used in the majority of all packaging applications. We fully agree with the TDMA/TDIC and CEPE positions of no classification of TiO2. The carcinogenic effect found exclusively in animal testing is based on particle-caused inflammatory processes in the lungs due to dust exposure by inhalation. However, this is not substance-specific for titanium dioxide but characteristic of a large number of dusts, irrespective of the underlying substance.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Gleitsmann Security Inks GmbH	BehalfOfAnOrganisation	152

Comment received
I represent the company Gleitsmann Security Inks GmbH established in Germany and respond on behalf of that company. We are a formulator of security printing inks and related products and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs about 75 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. There exists no alternative material with comparable properties (opacity, whiteness, …). With regard to the toxicological assessment we therefore strongly believe that the proposal is disproportionate to the risks posed to human health and would have serious negative impacts to our company as well as to the economy. ECHA note – A non confidential attachment was submitted with the comment above. doc20160712121001.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Spain	CIN Valentine S.A.U.	BehalfOfAnOrganisation	153

Comment received
As all coating producer companies, we have been using titanium dioxide for many years, being by far pigment number one of our purchasing portfolio. During these years, no cancers among our workers due to the use it have been reported. It is a key, basic element for all white and pale colours in all sectors where coatings is used, specially in the Decorative/Architectural sector. Once the proposed classification enters into force, this market for "do it yourself" will disappear, and, although it is very difficult to predict how the professional painter will react to the labelling as cancerogenic of the coating they have been using for years, we can estimate a 15-20% sales reduction. As far as we know, there are no real alternatives to titanium dioxide. As per our information, there are some scientific doubts about the implications on humans of the studies done on rats to evaluate carcinogenic properties of titanium dioxide, so our opinion is that no decision can be taken since a revision of this data is done.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	I&P Europe - Imaging and Printing Association e.V.	BehalfOfAnOrganisation	154

Comment received

I&P Europe – Imaging and Printing Association is a European association of product manufacturers, formulators, importers and technology providers for the imaging and printing industry. Our members' products include conventional and digital imaging and printing products and their processing solutions.
TiO2 is used in our industry for many years/decades in toners, inks, backings for inkjet printing substrates, coated layers on specialty foils, and incorporated into PET for some applications. Over this time span, no health and safety issues have been recorded by I&P Europe Member Companies resulting from the use of TiO2 either as a raw material or in their products brought on the market for professional- or consumer use.

• As a raw material TiO2 can be used in industrial environment in a controllable way, minimising the exposure to operator and to the environment, and respecting hereby the regulatory defined exposure levels. The long term exposure level through inhalation currently in place in many countries is 10mg/m³. A value which is 25 times lower than the air-borne concentration used during the 2 disputed rat carcinogenicity tests.
• Imaging and printing products sold on the market do not expose the users to inhalable or respirable forms of TiO2 dust, as the substance – which most of the time is used as white pigment – is embedded in the products in bound form. The proposed classification is based on inhalation exposure route, which is not relevant for the imaging and printing products. No free TiO2 was found under normal use conditions of said products.

Undeniably TiO2 currently is the most effective white pigment available for the imaging and printing industry. Alternatives for TiO2 have been tested, but no other white pigment matches the functional properties of TiO2 in the imaging and printing applications. Moreover all alternatives tested where also poorly soluble solid products, with similar particle size distributions as the TiO2 grades used.

• The unique pigment properties of TiO2 result from the very high refractive index it has compared to other white pigments (cfr. the figure below), which results in high light scattering properties.
• To obtain the same effect in pigmented materials with alternative substances such as zinc oxide, aluminium oxide or barium sulfate, resp. 4 to 6 times as much pigment (ZnO) or 10 to 14 times as much pigment (Al2O3 and BaSO4) would need to be added, amounts which are so high that the high pigment concentration results at one hand in a loss again in scattering properties because of 'crowding' at the percolation point and at the other in a loss in physical performance of the product (due to loss in mechanical strength of the pigmented matrix or viscosity increased or solidification of liquid products).
Less scattering properties by other pigments than TiO2 could also be replaced by deposition of (coating, inkjetting, …) thicker layers, but these layers are then more difficult / impossible to dry or cure, nor will they perform any longer the required functionalities.
(for further explanation please see picture in the document attached)

A possible classification of TiO2 as Cat 1b carcinogen is expected to have a series of consequences, such as:
• A loss of acceptance in the supply chain of imaging and printing products, making use of the pigment.

• Supply to consumers of inks and toners containing TiO2 would be prohibited. • End of life materials containing the carcinogen will pose big problems for re-use in a circular economy or in the treatment as waste. Ames test conducted for the mixtures of toner preparations with bound TiO2 show negative result indicating that the toner preparations are not mutagenic. Overall we fully support the TDMA / TDIC and VCI positions that a classification and labelling is completely unfounded. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf
Dossier Submitter's Response
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Stephan Schmidt KG	BehalfOfAnOrganisation	155
Comment received				
Statement on „CLH-report for Titanium Dioxide" 1. Preliminary note In its present form the CLH report seems to be unsuitable as a basis for classifying mineral TiO2 compounds as carcinogenic. In consideration of the world occurrence of rutile and anatase in natural soils and rocks and their extreme extension in everyday commodities (from wall paint to sunscreen to pills, as E171 as food additive and as pigment CI77891 in cosmetics), a much clearer differentiation has to be taken between natural TiO2 minerals, corresponding synthetic TiO2 variants and coated or surface-modified TiO2 compounds with regard to their carcinogenicity. Essentially, carcinogenic effects are triggered by the surface chemistry of the particles in the pulmonary tissue. If such inflammation-triggering interaction with the tissue occurs, this can be intensified by permanent irritations which can be attributed to the crystal form and the insolubility of the particles in the tissue fluid (e.g. in the case of asbestos fibres). The converse argument, i.e. to classify the insolubility of a particle in the first place of the hazard potential without any chemical examination, is not admissible. In this case any insoluble solid matter, irrespective of its chemical composition, would be carcinogenic! 2. Explanatory statement: In the present study four „alleged" TiO2 modifications are examined and characterized (p. 42). All these TiO2 modifications were generated synthetically. ☐ P25 is a mixture of –probably- uncontaminated and not coated rutile and anatase (that must be confirmed) ☐ uf-1 is classified as rutile, but with an unnatural impurity of Al (a stabilizer for the synthesizing process?) or a surface coating with Al. Therefore, it shouldn't be discussed in the same context with pure/natural/geogenic rutile/anatase. ☐ uf-2 is definitely a coated rutile. Therefore, the surface chemistry is definitely totally different from those of a rutile/anatase surface and cannot be connected in any way in concern to carcinogenicity. ☐ Fine TiO2: comparable to uf-1 because of its alumina content. In the section "Impurities" (p. 12) the indication of ingredients is omitted with the hint "Confidential". This means that the titanium dioxide compounds were generated synthetically, because in the case of geogenic rutiles / anatases the percentages of trace				

elements would not be concealed. Furthermore, on page 12 at the bottom, Al and Si compounds are characterized, which must not be linked with natural titanium dioxide minerals either. In conclusion, „synthetic impurities" must be characterized as such and therefore be differentiated from geogenic compounds. Thus it can be avoided that geogenic rutiles / anatases are classified as carcinogenic on the basis of values determined for synthetic TiO2 modifications.
Elements such as iron, vanadium, tin, niobium, tantalum and chrome in the order of XOO ppm are characterized as possible natural impurities in rutile / anatase / brookite (Rösler, Luvizotto), but neither silicium nor aluminium.
In the case of
☐ product uf-1 a transfer of the examination results regarding carcinogenicity to naturally occurring rutiles and anatases can be definitely excluded because the surface chemistry of this product does not correspond with that of rutile / anatase.
☐ products uf-2 and Fine TiO2 transferability of the results seems to be questionable because of their aluminium content, because aluminium is not characterized as component in natural rutiles / anatases.
3. Next steps:
We propose to extend the key points suggested by TDMA by the following points:
I. Declarative statement
a. that the surface chemistry of coated TiO2 modifications is completely different from that of pure TiO2 compounds (that is why they were coated), and therefore coated TiO2 compounds (q.v. table on p. 13) must be graded separately from uncoated TiO2 compounds.
b. that synthetic TiO2 modifications containing aluminium must be graded separately from geogenic TiO2 minerals.
II. Declarative statement that assumed or actual carcinogenicity caused by
a. coated TiO2 modifications must not by any means be transferred to geogenic TiO2 minerals
b. synthetic TiO2 modifications containing aluminium must not by any means be transferred to geogenic TiO2 minerals.
III. Removal of the reports on coated TiO2 modifications from the CLH report as being „not relevant for TiO2" for reasons mentioned in I. and II.
Literature
Rösler, H.J. (1983): Lehrbuch der Mineralogie; VEB Deutscher Verlag für Grundstoffindustrie, Leipzig; p.397-401
Luvizotto, George Luiz: Trace element signatures in rutile: characterization of standards and applications to accessory mineral behavior in metamorphic rocks •URN: urn:nbn:de:bsz:16-opus-89248 •URL: http://www.ub.uni-heidelberg.de/archiv/8924)

Dossier Submitter's Response

See points 1 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

Specific response: both natural and synthetic forms of TiO_2 are covered by the scope.

RAC's response

The scope of a harmonised classification extends to all substances covered by the substance identity that need to be registered or notified in accordance with the REACH Regulation.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Japan		BehalfOfAnOrganisation	156
Comment received				
Impact of a CMR IB classification on cosmetic products We have great concerns on negative implications for our business caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter as well as colorant cannot be put in use in market. Based upon the reasons mentioned in the specific comments, we concerned about the sentence: "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B-H350i", is lack of sound scientific evidence. (4.1.6, page 69) When IARC classified TiO2 in the Group 2B "possibly carcinogenic to humans", it didn't have any negative impact on our business since IARC does not limit the use of TiO2 as cosmetic ingredients. However, if TiO2 is classified as Carc. Cat 1B-H350i by CLP regulation, TiO2 cannot be used in cosmetics according to Article 15 of the Cosmetics Regulation 1223/2009, "the use in cosmetic products of substances classified as CMR substances (substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity), of category 1A or 1B under Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures. Thus, we would like to request the authorities to reconsider the classification of TiO2 based on more realistic exposure simulation since we believe TiO2 does not show carcinogenic potential under normal and foreseeable misuse conditions of cosmetics containing TiO2.				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		Individual	157
Comment received				
Although millions of people have been dealing with powderous TiO2 products in the last 100 years, there is not one proven case of lung cancer caused by TiO2 in humans. Inconsistent inhalation and insertion studies in animals are not an appropriate basis for making decisions like this one. Since TiO2 cannot be replaced as a pigment, and since TiO2 is only processed in professional working environments, a classification as a 1b carcinogenic would have no positive influence on anyones health. The economical impact on industry, TiO2 producers as well as TiO2 users, would not be justifiable. ECHA note – A non confidential attachment was submitted with the comment above. Comment to RAC of the ECHA Jochen Winkler.docx				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM. Specific response regarding EINECS list. EINECS is an inventory of substances that were deemed to be on the European Community market between 1 January 1971 and 18 September 1981. There is no toxicological assessment for inclusion of a substance in this list. Indeed, substances including in this list can also have a CMR classification (for example, formaldehyde).				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Japan	JTDIA (Japan Titanium Dioxide Industry Association)	BehalfOfAnOrganisation	158

Comment received

The authority which has classified Titanium Dioxide as suspected human carcinogens is IARC with no other followers as shown in following list of classifications published by several authorities:

IARC (International Agency for Research on Cancer):
Classified as 2B (Possibly Carcinogenic to human)

Japan Society for Occupational Health:
No classification (Classification not possible)

ACGIH (American Conference of Governmental Industrial Hygienists):
A4 (Category of materials which can not be classified)

NTP (National Toxicology Program):
No report (Classification not possible)

As the reason of possible carcinogenicity of Titanium Dioxide to human, IARC stated that lung tumours were found after inhalation exposure in rats. However studies show no tumour occurrence in mice and hamsters, furthermore epidemiological group studies conducted in Europe and North America show no cause-effect relationship between Titanium Dioxide and carcinogenicity. Therefore, we have concluded that "the reasons provided by IARC are not sufficient evidence for the carcinogenicity of Titanium Dioxide to human".
It is to be a long term issue which requires a lot of verifications for conclusion whether the results pointed out by IARC from the experiments on animals are acknowledged or not by other authorities as the carcinogenic risk to human. It is indeed current reality that "sufficient information has not been obtained about the Titanium Dioxide carcinogenicity".
Carcinogenic classification 1B (equivalent to IARC classification 2A) proposed by France is stipulated on the conditions; "Exposure to Titanium Dioxide causes cancer in experiments on animals" and "The mechanism of the carcinogenicity can be applied to human, too".
On the other hand, carcinogenic classification 2 (equivalent to IARC classification 2B) is on the conditions; "Exposure to Titanium Dioxide causes cancer in experiments on animals" but "The mechanism of the carcinogenicity can't be applied to human".
It is not reasonable for the French institute to classify Titanium Dioxide as carcinogenic 1B because of the presence of the above quoted epidemiological group studies in Europe and North America. In addition, there are no new contents found to conclude the carcinogenicity of Titanium Dioxide in the French CLH report.
In conclusion, it is to be too early for ECHA and RAC to positively recognize the carcinogenic classification proposed by France. We appreciate sound regulation for industrial development, but we are against the proposals which inhibit industrial progress by immoderately stirring up the risk.

Organisation:
JTDIA (Japan Titanium Dioxide Industry Association)

(ISHIHARA SANGYO KAISHA, LTD. ,SAKAI CHEMICAL INDUSTRY CO.,LTD., Titan Kogyo,Ltd. , TAYCA CORPORATION, FUJI TITANIUM INDUSTRY CO., LTD. and FURUKAWA CHEMICALS CO.,LTD.)
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Australia	Australian Paint Manufacturers' Federation Incorporated	BehalfOfAnOrganisation	159
Comment received				
Comments are attached. ECHA note – A non confidential attachment was submitted with the comment above. ECHA Proposed Classification of Ti02.pdf				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Japan	Japan Cosmetic Industry Association	BehalfOfAnOrganisation	160
Comment received				
Impact of a CMR IB classification on cosmetic products We have great concerns on negative implications for cosmetic industry caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter in sunscreen products cannot be put in use in market. Based upon the reasons mentioned in the specific comments, we concerned about the sentence: "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B-H350i", is lack of sound scientific evidence. (4.1.6, page 69) When IARC classified TiO2 in the Group 2B "possibly carcinogenic to humans", it didn't have any negative impact on cosmetic industry since IARC does not limit the use of TiO2 as cosmetic ingredients. However, if TiO2 is classified as Carc. Cat 1B-H350i by CLP regulation, TiO2 cannot be used in cosmetics according to Article 15 of the Cosmetics Regulation 1223/2009, "the use in cosmetic products of substances classified as CMR substances (substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity), of category 1A or 1B under Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures. Though such substances may be used in cosmetic products by way of exception where all of the conditions addressed in the article are fulfilled, none of substances have been exempted by fulfilling them all to date. Thus, we would like to request the authorities to reconsider the classification of TiO2 based on more realistic exposure simulation since we believe TiO2 does not show carcinogenic potential under normal and foreseeable misuse conditions of cosmetics				

containing TiO2.
Dossier Submitter's Response
See points 4 and 5 of the attachment to the RCOM
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	BASF	BehalfOfAnOrganisation	161
Comment received				
I represent BASF companies established in France, state member of the EU and I answer on behalf of these entities. BASF is a major user of titanium dioxide and co-registrant in the joint REACH registration dossier. Titanium dioxide is used by BASF as raw material in the production of inorganic pigments and as filler and toner component in preparations. BASF is not a manufacturer of Titanium dioxide. BASF considers that the classification in Category 1B (inhalation) is not justified. In the CLH report, the comparison between criteria in section 3.6.2 of the CLP directive and the available data is not conclusive. Requirements on the strength of evidence regarding human relevance are not clearly depicted and the evidence against human relevance is not adequately taken into account. It is expected that a re-assessment according to the CLP criteria would generate additional clarification. BASF therefore recommends to reject this proposal.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Portugal	CIN - Corporação Industrial do Norte, S.A.	BehalfOfAnOrganisation	162
Comment received				
Titanium Dioxide has been used in our company for several decades. We have bought many thousands tons and we don't have any evidence of respiratory cancers in workers that handled TiO2 for many years. It is a very important raw-material in the paint industry and we estimate a 15 to 20 % decrease on Decorative Sales. Actually the general public market is growing but the proposed classification will not permit the consumer application, eliminating this market. Our technical department doesn't have any alternatives to TiO2 in order to avoid the huge impact that this proposal will have in our company, especially in the Decorative business but also in the Industrial and Protective Coatings business. We think that the toxicological and epidemiological studies should be re-evaluated because real life data does not confirm the ANSAES conclusions.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Netherlands	PPG	BehalfOfAnOrganisation	163
Comment received				
The existing scientific information supports the conclusion that TiO2 should not be classified as a human carcinogen and the unnecessary classification of TiO2 as a human carcinogen would have significant negative implications. TiO2 is an essential ingredient in white and light colored coatings products. The proposed classification of TiO2 as a carcinogen will require all paints formulated with TiO2 in the EU to be classified as carcinogenic and, as there are no known technical alternatives, 75% of paint products will no longer be available to household consumers. In other non-consumer market segments, customers may refuse TiO2 containing products because of unwarranted concern over the safety of such products. The specific comments given below outline how the available scientific information does not support the classification of TiO2 in its pure form as a human carcinogen. There is even less basis for the classification of TiO2 as a carcinogen when in a mixture such as a liquid coating. In liquid coatings, the TiO2 particles are embedded in a liquid matrix and bound up in the cured coating film; as a result, there is no meaningful potential for human exposure to unbound particles of TiO2. In 2011, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency added TiO2 as a carcinogen to the list of chemicals requiring warnings for chemicals known to the State of California to cause cancer, birth defects or other reproductive harm under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (commonly referred to as Proposition 65 or Prop 65), but only when it pertains to airborne, unbound particles of respirable size. This listing mimicked an earlier listing of carbon black as airborne, unbound particles of respirable size. OEHHA justified this decision by stating that "exposure to carbon black, per se, does not occur when it remains bound within a product matrix, such as rubber, ink or paint." Therefore, if TiO2 is classified as a human carcinogen the classification should be limited to unbound particles of respirable size.				
Dossier Submitter's Response				
See point 1 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	German Ceramic Raw and Industrial Minerals Association	BehalfOfAnOrganisation	164
Comment received				
In its present form the CLH report seems to be unsuitable as a basis for a harmonised classification and laballing of titanium dioxide as Carc. Cat. 1B - H350i. TiO2 in form of rutile and anatase is a general mineral component of clay like other non-phyllosilicates, for example quartz or feldspar, in concentrations up to 4% (w/w). Rutile is the most abundant of the three naturally occurring forms of titanium dioxide. The other two being anatase and brookite. Clays and even kaolins containing rutile and anatase are ubiquitous. The disproportionate conclusions on classification and labelling have far-reaching effects for our stakeholders, for example the agricultural industry (fertilizers and soil improvers) or the ceramic and refractory industry. It is very important to distinguish between naturally occurring TiO2 and manufactured				

ones, especially coated titanium dioxide (chemical and surface treated), which is the basis for the mentioned carcinogenetic studies. The classifiable substance, the substance identity, based on the registration dossiers, and the tested substances are not equal. We therefore call for clarification!

The hazard view and the risk view are mixed. On the one hand we are talking about titanium dioxide in all phases and in all particle sizes and on the other hand we are talking about a classification only for fine particles and nanomaterials of TiO2. We therefore call for clarification!

Furthermore depending on a validated carcinogenic classification of titanium dioxide not only for the tested substances, a threshold value for the inhalation route for the three naturally occurring forms of titanium dioxide must be checked! We therefore call for a comment!

Dossier Submitter's Response

See points 1, 2 and 5 of the attachment to the RCOM.

Specific response: both natural and synthetic forms of TiO_2 are covered by the scope.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Motip Dupli GmbH	BehalfOfAnOrganisation	165

Comment received

TiO2 has been used by our company for decades with its presence within the major part of our product range without causing any problem and no identified health concerns. As there is no substitute raw material available the intended classification will lead to a drastic reduction of our product offer. Consequently it would cause a major loss of business and jobs. In practice this means that consumer products like white wall paint would fall under the ban of the sale to the general public according to REACH.

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	WEILBURGER Graphics GmbH	BehalfOfAnOrganisation	166

Comment received

I represent the company WEILBURGER Graphics GmbH established in Germany and respond on behalf of that company. We are a formulator of paints and coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 115 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.

Dossier Submitter's Response

See point 5 of the attachment to the RCOM.

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	Aspa-Ingrecos	BehalfOfAnOrganisation	167

Comment received

Aspa-Ingrecos is the French national trade union of surfactants and cosmetic ingredients manufacturers, a member of EFfCI, European Federation for Cosmetic Ingredients at European level.
Titanium Dioxide is widely used in cosmetics and manipulated by workers in plants for many years without any adverse effects observed.
According to the ANSES' report (page 8) towards carcinogenicity, human data do not suggest an association between occupational exposure to TiO2 and risk for cancer.
This is the reason why we wonder ANSES' proposal to classify TO2 Carcinogenic 1B by inhalation.

Regarding the CLP criteria (regulation 1272/2008), a substance is classified Carcinogenic category 1 (known or presumed human carcinogens) only on the basis of epidemiological and/or animal data ;
And the substance may be further distinguished as:
Category 1A: known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B: presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.
Titanium Dioxide cannot be classified carcinogenic category 1A because human data do not suggest an association between occupational exposure to TiO2 and risk for cancer.
Titanium Dioxide would not be classified carcinogenic category 1B because animal data do not constitute an enough strength weight of evidence.
Anses's report mentions 4 inhalation route studies on animal : Lee, 1985 ; Heinrich, 1995 ; Muhle, 1989 and Thyssen 1978.
Only two out of four show positive results :
- In Heinrich's study : impairment of clearance function, bronchioalveolar hyperplasia and interstitial fibrosis observed in female rats ; and not carcinogenic in female mice ;
Not guideline, no GLP status study : cannot be scored 1 according to Klimisch

- In Lee's study : males and females rats tested : impairment of clearance function, pulmonary inflammation and cell proliferative responses from 50 mg/m3
Similar to guideline, no GLP status : score according to Klimisch ? (probably not 1)
Relevance of these higher doses : 50 and 250 mg/m3 compared to doses in the cohort study (Chen et al., 1988) up to 20 mg /m3 level of TiO2 at which workers are exposed.
We would like to quote page 51 the following paragraph :

''Based on these studies, IARC (2010) classified TiO2 as possibly carcinogenic to humans (Group 2B) without differentiation between ultrafine and fine TiO2 particles. However, based on the same studies, the NIOSH (2011) concludes that although ultrafine TiO2 should be considered a potential occupational carcinogen, there are insufficient data at this time to classify fine TiO2 as a potential occupational carcinogen since effects were observed at concentration (250 mg/m3) that was significantly higher than currently accepted inhalation toxicology practice. ''

We are not certain that Lee's study alone can justify the ANSES' proposal to classify TiO2 carcinogenic category 1B. Doses in Lee's study are exceeding the maximum tolerated

dose and leads to the overload lung phenomenon which seems normal at these excessive doses (250mg/m3). In consequence, the strength of evidence is too low to consider the ANSES' proposal to classify TiO2 as carcinogenic category 1B by inhalation.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Belgium		BehalfOfAnOrganisation	168
Comment received				
I represent the company <confidential> established in the EU Member State Belgium and respond on behalf of that company. We are a formulator of industrial coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 50 people. We have been using this substance for 47 years. As we successfully manage the workplace exposures of dust (refer to aspect 2 detailed in page 1), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public, refer to aspect 3, detailed in page 1) and to our company' (refer to aspect 4, detailed in page 1)				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	HAGHEBAERT ET FREMAUX	BehalfOfAnOrganisation	169
Comment received				
Je représente la société HAGHEBAERT ET FREMAUX établie en France, État membre de l'UE et je réponds au nom de cette société. Nous sommes formulateur de peintures pour l'industrie et les professionnels du bâtiment. Notre société emploie actuellement 45 personnes. Nous sommes gravement préoccupés par la proposition faite par la France de classer le dioxyde de titane comme cancérogène. Nous utilisons cette substance depuis la création de la société en 1907. Nos postes de travail sont équipés d'aspirations à la source, limitant considérablement l'inhalation de poussières par les travailleurs, comme le démontrent les mesures d'exposition réalisées. Depuis la création de la société, aucune maladie professionnelle n'a jamais été portée à notre connaissance et donc aucune liée au dioxyde de titane. Le TiO2 est un matière première clé dans la fabrication de nos produits. Il est utilisé en tant que pigment blanc et entre dans la composition des peintures blanches et des peintures de teintes non vives. Il n'existe pas de substance de substitution à notre connaissance ni celle de nos fournisseurs. Etant donné la quantité de dioxyde de titane présente dans nos formulations, la				

classification proposée affecterait également les peintures que nous commercialisons. Or une classification cancérogène de nos peintures impliquerait l'interdiction de vente au grand public et l'obligation pour nos clients de manipuler nos produits en vase clos, ce qui est impossible. Ce projet ne semble pas pertinent, étant donné que le dioxyde de titane lié dans une peinture liquide n'émet pas de poussière, au même titre que l'inhalation de poussières de bois présente des risques alors que la manipulation du bois brut n'en présente pas. Une fois la peinture appliquée et sèche, la combinaison du support et du film de peinture confère à l'objet fabriqué, le statut d'article. L'évaluation des risques liés à l'inhalation des poussières lors d'opérations de ponçage est à considérer dans son ensemble et en dehors du cadre du règlement CLP. Nous considérons que l'évaluation d'une toxicité éventuelle par inhalation pour un utilisateur final doit être menée dans le cadre d'une évaluation des risques liée à l'exposition de l'utilisateur final à ces poussières durant une opération de ponçage – poussières qui peuvent contenir du TiO2 mais n'en sont pas exclusivement constituées, ou ne pas en contenir selon la nature des supports et de leur finition. Si cette classification était retenue, nous serions contraints d'arrêter la fabrication de peintures. L'impact sur notre activité d'industriel de la chimie serait beaucoup plus important que dans d'autres secteurs industriels, du fait des règles de classification des mélanges définies dans le règlement CLP, applicables uniquement aux produits chimiques. Dans notre cas, toute la chaîne d'approvisionnement serait impactée, jusqu'au client final.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom	Sun Chemical Europe	BehalfOfAnOrganisation	170
Comment received				
Titanium dioxide has a long history of safe use within our industry. It is a very widely used, ubiquitous white pigment. We have seen no evidence that exposure to titanium dioxide causes cancer amongst our workers, or within our industry. Our industry uses many pigments, which can be regarded as poorly soluble dust particles. Exposures are readily controlled by engineering measures and with respiratory protective equipment if necessary, to protect against inhalation of dusts. Once the pigments are incorporated into our products, there is no scope for inhalation of particulates. Titanium dioxide is already the safest white pigment available - other white pigments are considerably more toxic, being based on heavy metals such as lead, barium and antimony. A carcinogenic classification for titanium dioxide has automatic consequential restrictions on use, which will prove impossible to replace. Virtually any item that is white will contain titanium dioxide: the socio-economic impact of the loss of all of these materials will be very large indeed. In summary, we believe that the proposal to classify titanium dioxide as carcinogenic is not supported by the evidence, and the consequences of such a classification will be very severe, and cause a large disruption to society.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	H. Schmincke & Co. GmbH & Co KG	BehalfOfAnOrganisation	171

Comment received
We are a manufacturer of artist colors using titanium dioxide as raw material for our products. The company H. Schmincke & Co. is established in the EU Member State Germany. I respond on behalf of that company and we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 75 people. We have been using titanium dioxide in powder form for many years by successfully managing the workplace exposures of dust through permanent measures and controlled air exchange in combination with appropriate personal protective equipment. Based on this more then 80 years experience of using titanium dioxide we are not aware of any relation to the development of cancer by our workers. Titanium dioxide is a key material to manufacture our products. The proposed classification would also affect all chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our titanium dioxide products artist colors have to face a direct or indirect loss in sales either through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards. Please see also our confidential attachment.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	Société BIC	BehalfOfAnOrganisation	172

Comment received
If TiO2 is classified carcinogenic 1B, it would have big impact for BIC industry: - European Toy Safety Directive forbids the use of carcinogenic substances in toys. BIC uses TiO2 in the leads of all their coloring pencils (BIC & Conté), in all their crayons (BIC), and even in plastic materials of their coloring felt pens (BIC & Conté) as colorant. As a consequence, it would also be no longer possible to sell these coloring products. - REACH restriction, entry N°28, forbids the use of substances classified as carcinogenic 1b above the classification threshold in mixtures for supply to the general public. BIC uses TiO2 to manufacture correction fluids (BIC & Tipp Ex). As a consequence, Tipp Ex and BIC Correction fluids wouldn't be allowed on the market anymore. - European Cosmetic Regulation forbids the use of carcinogenic substances in cosmetics. BIC uses TiO2 in lubra strips which are assessed according to this regulation. As a consequence, it would be no longer possible to sell shavers with lubricating strips. In all these types of products total substitution is technically impossible as colorant, opacifying agent, strong UV protector. BIC products are evaluated by a toxicologist based on exposure (risk). Such a

classification would reflect a hazard and not a risk based on the exposure. The consequence would be for BIC the ban of commercialization of their coloring products and correction fluids and their shavers which have been assessed as safe for the consumer by the toxicologist. BIC is using other poorly soluble dusts as raw materials. If similar classification should be applied to these substances too, it would impact much more our industry. After reviewing TDMA technical data, BIC fully supports and agrees with the TDMA/TDIC position of no classification of TiO2.
Dossier Submitter's Response
See points 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Boehringer Ingelheim	BehalfOfAnOrganisation	173
Comment received				
Boehringer Ingelheim as a research driven pharmaceutical company fully supports the comments on the proposed harmonized classification of titanium dioxide that were submitted by the German Chemicals Industry Association (VCI). We follow the argumentation that this proposal for classification is based on inappropriate toxicological assumptions and would result in serious negative impacts for the pharmaceutical industry. More information is summarized in the attached pdf document. For reference to our industry and the special concerns we have as a company please directly refer to chapter "Use of titanium dioxide in the pharmaceutical industry" on page 3 of the attachment. ECHA note – A non confidential attachment was submitted with the comment above. Statement_TiO2.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Denmark	Haldor Topsoe A/S	BehalfOfAnOrganisation	174
Comment received				
Haldor Topsoe A/S supports and agrees with the TDMA/TDIC position of no classification of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Cyprus		BehalfOfAnOrganisation	175
Comment received				
I comment on behalf of a company producing and selling coatings and inks. Knowing the importance of titanium dioxide in our sector, our company is very concerned about the proposal for classifying it as a carcinogen, since we have been producing and selling a very long range of coatings and inks for more than 40 years. We strongly disagree with this classification for the following reasons: 1)After a very long history in the production of coatings and inks, we are not aware of any relation between the use of titanium dioxide during the manufacture and the appearance of cancer in any of our workers. 2)We believe that the dust masks used as a personal protective equipment by our workers during handling any material in the physical state of dust, should be enough and mandatory to protect from any dust related material. This should be enough for the case of titanium dioxide, too and it is a procedure already followed for all materials of this phyical state. 3)In relation with the previous point, although the end-user of the final liquid product, either that would be a coating or an ink, will not be in danger of coming in to contact with titanium dioxide dust, will be strongly affected by the decision of classifying it as a carcinogen, since this would cause an enormous problem to the companies producing the inks and coatings. The end-user may be an individual (for example someone to paint his house) or a company (for example a printing company), but both will be affected negatively by the classification of titanium dioxide as a carcinogen. 4)The titanium dioxide is one of our most important raw materials. The proposed classification would have a high impact in our company and the general public. This may include a potential ban on the production and sale of most inks and coatings (for any substrate, including wall, roof, wood, metal, plastic etc), since it is not only used for white products, but also for other colored products in order to achieve the desired color and the coverage of the substrate. The high economic impact this might cause, will not only be for our company, but for the whole market and end-users as well. We look forward to the reversal of the proposal for classification of titanium dioxide a a carcinogen.				
Dossier Submitter's Response				
See points 1, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany		BehalfOfAnOrganisation	176
Comment received				
TDMA/TDIC Working Draft Commentary on CLH report Status: 03-JULY-2016 The scientific objections set out in the above-mentioned comments are convincing arguments against the given classification proposal. (Carc. 1B – H350i)				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany		BehalfOfAnOrganisation	177
Comment received				
I represent the company <confidential> established in Germany [EU Member State] and respond on behalf of that company. We are a formulator of wood coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 75 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Poland	Caparol Polska Sp.z o.o.	BehalfOfAnOrganisation	178
Comment received				
Caparol Polska is both producer and distributor of water borne paint, and plaster. We distribute paint for over 20 years and we produce with the use of Titanium Dioxide since 2010. TiO2 is one of the clue ingredients of our products. Private consumer, which is the end user, is not exposed to titanium dioxide powder. Consumer receive the ready-to-use product with dioxide already incorporated. There is no risk of powder inhalation. We are not aware of any cancer cases among: factory workers, building-site workers, and the consumer using the product. Change of classification would be surely uneconomical and above all would be a huge technological step backwards for all industries using TiO2 as a clue ingredient. There is no substitutional compound with comparable parameters. In our opinion, titanium dioxide powder is not harmful for human, especially not for the consumer that have no possibility of exposure to the powder. We fully support the position for no Labelling the TiO2.				
Dossier Submitter's Response				
See points 1 and 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Poland	Polifarb Łódź Sp.z o.o.	BehalfOfAnOrganisation	179
Comment received				
We are company which operates In the paint industry Since 1946. We produce a wide range of paints, enamels and varnishes (waterbased and solventbased). TiO2 is our key material to manufacture our products and it is used in our company for at least 50 years. During this time we have never had information of health problems (cancer) among our employees, which were associated with exposure to TiO2. Workers exposure to TiO2 and other dust is reduced by using ventilated compartment provided adequate ventilation. Our workers also use protective equipment (respiratory protection				

and protective cloth) and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. The proposed classification will cause serious problems for producers of paints, because there are not alternative products available.
Dossier Submitter's Response
See points 1, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France		Individual	180
Comment received				
I represent the LYD France company established in France, Member state of the EU and I answer to the name of this company. We are a manufacturer of paints and we are worried by the proposal made by France to classify the dioxide of titanium as carcinogenic. Our company employs at present 13 people. We use this substance since the middle of the 80s. Ensuring, successfully the management of the exposures dusts in the workplace, we have no knowledge of a relation between the use of the TiO2 and the development of cancer at our workers. The TiO2 is a key raw material in the manufacturing of our products. It finds itself in 15 % a 25 % of our products. The proposed classification would also allocate chemical mixtures and we believe firmly that this would be disproportionate, with a strong economic impact on our markets (general public, industrialist, professional, community). To our knowledge, the risk is connected to the inhalation of the dust of TiO2 and not to the mixture containing of the liquid-phase TiO2. The economic impact would be very also on our company, because to our knowledge, there is no substitute product in the TiO2.				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	Fédération Française de Photocatalyse	BehalfOfAnOrganisation	181
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom		BehalfOfAnOrganisation	182
Comment received				
Apparently, the studies referred in the dossier were not conducted in GLP labs and some of them admittedly do not fulfill any international standards therefore their relevance is questionable. Also, the findings of the studies do not seem to be strong enough to support intrinsic carcinogenicity.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	hubergroup Deutschland	BehalfOfAnOrganisation	183
Comment received				
I represent the company hubergroup Deutschland established in Germany and respond on behalf of that company. We are a formulator of printing inks and related products and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs about 1000 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. There exists no alternative material with comparable properties (opacity, whiteness, …). Without Titanium Dioxide White printing inks will not be available in the same quality anymore. This might even have an influence on quality and safety of food packaging, as the white printing ink layer is not only used for decorative reasons but also e.g. for protection against degradation by light. With regard to the toxicological assessment we therefore strongly believe that the proposal is disproportionate to the risks posed to human health and would have serious negative impacts to our company as well as to the economy ECHA note – A non confidential attachment was submitted with the comment above. hgD Statement_ECHA_Consultation_TiO2.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom		BehalfOfAnOrganisation	184
Comment received				
<confidential> are a supplier and UK manufacturer of wall decoration products. We supply consumer goods to DIY retailers globally. Titanium dioxide is an essential ingredient in our products it is used as a white pigment and also to improve opacity. There are alternatives but these are not as efficient. We do				

not use Titanium Dioxide in the powder form on site it is contained in our plastisol, inks and coatings. The titanium dioxide is locked in to the finished goods and poses no risk to consumers. We support the TDMA scientific data.
Dossier Submitter's Response
See point 1 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Harold Scholz & Co. GmbH	BehalfOfAnOrganisation	185
Comment received				
We are a formulator of pigments using titanium dioxide as raw material for our products. The company Harold Scholz & Co. GmbH is established in the EU Member State Germany. I respond on behalf of that company and we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 190 people. We have been using titanium dioxide in powder form for many years by successfully managing the workplace exposures of dust through permanent measures eg. controlled air exchange in combination with appropriate personal protective equipment. Based on more than 20 years experience of using titanium dioxide we are not aware of any relation to the development of cancer by our workers. Titanium dioxide is a key material to manufacture our products. The proposed classification would also affect all chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our titanium dioxide products eg. Producers of pigment preparations, masterbatches, paints and concrete have to face a direct or indirect loss in sales either through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards.				
Dossier Submitter's Response				
See points 1, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	xxx	BehalfOfAnOrganisation	186
Comment received				
Je représente la société xxx établie en France, État membre de l'UE et je réponds au nom de cette société. Nous sommes fabricant de produits pour le second œuvre bâtiment comme les enduits de façade, les mortiers de sol, les produits de mise en œuvre du carrelage ou les produits de réparation ou de protection du béton et nous sommes préoccupés par la proposition faite par la France de classer le dioxyde de titane comme cancérogène. Notre société emploie actuellement 200 personnes. Nous utilisons cette substance depuis les années 1970. Nous travaillons depuis plusieurs décennies pour diminuer l'exposition aux poussières de nos personnels à travers des protections collectives (extractions avec dépoussiéreurs), des protections individuelles (masques à ventilation assistés) et la conception de nos				

nouvelles installations industrielles. Nous n'avons jamais eu à déplorer une relation entre l'utilisation du TiO2 et le développement de cancer chez un de nos salariés.
Le TiO2 est une matière première technique clé dans la formulation de nos produits et nous ne pouvons pas facilement substituer le TiO2.
Le TiO2 permet d'opacifier les revêtements de surface et nécessiterait de fortement augmenter les épaisseurs de film déposées avec des impacts induits sur l'hygiène et l'environnement.
Le TiO2 permet également d'obtenir des couleurs très blanches qui font le charme de certaines de nos régions.
La classification proposée aurait un fort impact économique sur nos marchés grand public et professionnel puisque nous ne pourrions plus vendre ces produits qui représentent 25% de notre Chiffre d'Affaires.
La classification proposée concerne le produit sous forme de poudre. Or dans le cas particulier des produits liquides ou pâteux qui ne génèrent pas, à l'utilisation, de poussières ou d'émissions d'aérosols, la classification proposée entrainerait automatiquement la même classification pour nos produits finis alors que le TiO2 ne peut pas être inhalé car il est pris dans la matrice liquide ou pâteuse de nos produits. La proposition de classement entrainerait la classification de nos produits liquides ou pâteux pour un danger (cancérogène par inhalation) auquel l'utilisateur n'est pas exposé durant l'utilisation au vu de l'état physique de ces produits, nous pensons que ceci serait disproportionné.

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom	British Coatings Federation	BehalfOfAnOrganisation	187

Comment received

The British Coatings Federation (BCF) is the trade association representing the UK's paints, coatings, printing inks and wallcoverings manufacturers, and is one of the largest users of titanium dioxide (TiO2), along with the plastics and paper industries. Our industries supply the construction, home improvement, printing, automotive, aerospace and other advanced manufacturing sectors worth over £150 billion to UK plc which employ more than 1 million people. TiO2is a constituent of over 85% of our members' products and thus any change to its classification will have a wide scale impact on our industry and on society.

We are aware that the public consultation on the proposed classification should only consider toxicological arguments on inherent properties, and we refer to the work done by the TiO2 manufacturers, which we support. TiO2 is a ubiquitous substance used safely for over 90 years for the decoration and protection of everyday household items, buildings, transportation, food and drink, and to prevent humans from developing skin cancer. It provides key properties to our products, such as whiteness, opacity, brightness, protection from UV light, stability and durability. It is the best way to provide an opaque white or coloured layer for decoration and protection for walls, metal objects, wooden trim and furniture, plastic films, and other substrates.

We would like at this early stage to alert Authorities to the consequences that a classification for TiO2 as a Carcinogen category 1B would cause. The consequences of the proposed classification would clearly be disproportionate to the actual risks posed to

human health. Across all sectors, there is no alternative to TiO2 that provides equivalent levels of performance – the quality, security in terms of health and welfare, and maintenance requirements for our surroundings, would change radically if TiO2-containing products were banned. Without it, there would be no decorative paints for consumers, an increase in food waste due to inferior packaging, and an increase in skin cancer because sun cream would become obsolete.

The risks to workers in our members' manufacturing industries are already highly controlled by the use of ventilation / extraction systems, and the proper use of PPE. There are no known cases of direct links between people being exposed to TiO2 in the workplace and occupational cancer, and there are no risks to consumers once the TiO2 powder is dispersed into a finished consumer product. A report by the European Centre for Ecotoxicology and Toxicology of Chemicals stated there is no indication of a positive association between occupational exposure to TiO2 and death from all causes, all cancers, lung cancer, non-malignant respiratory disease or all heart disease. The epidemiology studies did not show an increase in lung cancer in the TiO2 workforce as a result of exposure to TiO2 dust.

If this substance becomes classified as a category 1B carcinogen, then due to the hazard-based nature of our chemicals legislation, there would be a wide-ranging negative impact on society and our economies. Most importantly, we refute the evidence submitted, as it contradicts modern studies and epidemiological evidence that suggest Ti02 is safe. TiO2 is an essential building block in paint and ink formulations, and without it the sector would be unable to function in a proper and responsible manner.

We remain available to provide further information.

ECHA note – A non confidential attachment was submitted with the comment above.
BCF TIO2 Consultation Response.docx

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France		BehalfOfAnOrganisation	188

Comment received

We work with Titanium dioxide since a long time and our workers does not have diseases linked to titanium dioxide. We protect them with PPE.

Dossier Submitter's Response

See points 2 and 4 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Belgium	European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)	BehalfOfAnOrganisation	189

Comment received

ECETOC TF `Lung Overload`
Letter of Opinion
13 July 2016

Opinion of ECETOC Task Force "Poorly Soluble Particles/Lung Overload" on whether tumour development seen in the rat following lung overload
of PSPs has any relevance for human health.

The members of the former ECETOC Task Force on Poorly Soluble Particles / Lung Overload (ECETOC Technical Report 122, 2013 available at http://bit.ly/ecetoc-tr122-pdf) have been asked by various member companies manufacturing TiO2 to provide a brief scientific comment on the appropriateness of the proposal from the French MSCA to classify the poorly soluble particulate substance Titanium Dioxide (TiO2) for Carcinogenicity Category 1B by inhalation from a scientific perspective. In particular, to address if the proposed classification is consistent with the scientific opinion of the ECETOC TF regarding potential health effects in man following inhalation exposures to poorly soluble particles (PSPs) such as TiO2.
This document provides a response to this request by highlighting current scientific knowledge regarding species-specific pulmonary pathological responses during chronic inhalation exposure to PSPs. For more detailed information a copy of the Task Force report is freely accessible on the ECETOC website (www.ecetoc.org).

The basic question about whether or not the rat is an appropriate model for the extrapolation of `lung overload` related pulmonary effects such as tumours to humans was addressed extensively in the ECETOC Task Force report that came to the following conclusions:
• "The rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload".
• "The rat lung overload findings [only observed at excessive exposure concentrations] is not a reliable predictive model in particular for [lung] neoplasia"
• "There were no compelling studies or a weight of evidence that would allow the ECETOC TF to conclude that the rat lung overload finding is a reliable predictive model, in particular for neoplasia, with regard to hazard or risk assessment for humans who are exposed to poorly soluble particles".

The basic conclusion reached by the ECETOC Task Force that tumour development in the rat following lung overload of low soluble particles is not relevant for human health is based on various conclusions explained in the Task Force Report and summarised below:
• The rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload.
• Lung tumours have to be regarded the final phenotypic `adverse outcome` only in rats, whereas in other species non-neoplastic lesions seem to be the respective `adverse outcome`.

• Humans are less sensitive to `lung overload` as epidemiological studies thus far have not been able to detect an association between occupational exposures to poorly soluble particles of low toxicity and an increased risk for lung cancer.
• The divergence in the largely common mechanistic sequence of the adverse outcome pathway may be related to a biological diversity of detoxification systems, especially in species specific anti-oxidant defences resulting in a more pro-inflammatory environment in rats compared to a more anti-inflammatory environment in other rodent species.
• The measured differences of particle retention, distribution and clearance patterns in the lungs of exposed rats vs. primates or humans, may account for both the greater sensitivity in rats and corresponding differences in pulmonary pathological responses to long-term particle exposures
• Slight differences in the bio solubility of deposited "poorly soluble particles" in biological fluids may influence chemical dissolution and based hereupon accelerate or slow down the process of lung overload development.
• Independent of particle size, inhalation exposure to high concentrations of low soluble particles of low toxicity are eliciting comparable localised pulmonary toxicity via processes that are pro-inflammatory in nature, causing oxidative stress and an persistent pulmonary inflammatory response.
• The mechanisms leading to an oxidative and inflammatory pulmonary status are clearly threshold related.
• There is no "nanoparticle-specific lung overload toxicity" and mechanistic findings for conventional "micro" particles apply also for nanostructured particles.

For the reasons summarised above, the ECETOC Task Force is of the scientific opinion that pulmonary toxicity, and in particular tumour development seen in rat lung following chronic inhalation exposures to PSP at doses producing lung overload is not relevant to human health.
On behalf of the ECETOC TF on "Poorly Soluble Particles / Lung Overload"

<confidential> Clariant, DE
<confidential> Shell, NL
<confidential> Wacker Chemie, DE
<confidential> Fraunhofer ITEM, DE
<confidential> Evonik, DE
<confidential> Cranfield University, UK
<confidential> DSM, NL
<confidential> BASF, DE
<confidential> ToxMinds, B
<confidential> Solvay, B
<confidential> Dupont, USA
<confidential> ECETOC, B

References
ECETOC (2013): Poorly Soluble Particles / Lung Overload, Technical Report 122

ECHA note – A non confidential attachment was submitted with the comment above.
ECETOC Cover Letter and Letter of Opinion.doc

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France		BehalfOfAnOrganisation	190
Comment received				
I represent a company established in France, state member of the EU and respond on behalf of this company. We formulate coatings and we are concerned about the french proposal to classify titanium dioxide as a carcinogen. Since the 80's (date of significant use of TiO2), our company has never had a reported case of cancer in its numbers caused by the inhalation of TiO2 in the manufacture of coatings. Our operators handling of powders during the manufacturing coatings are protected by suction systems of dust regularly cleaned. In addition, they wear anti dust masks as individual protective equipment. Titanium Dioxide is an essential raw material for the paint, coatings and ink industries, and is used in over 80% of our products. It provides key properties to our products, such as whiteness, opacity (hiding power), brightness, protection from UV light, sustainability and impact washability, stain resistance. It is the best way to provide an opaque white or coloured layer for decoration and protection for walls, metal objects, wooden trim and furniture, plastic films, and other substrates. The proposed classification would also affect the chemical mixtures and firmly believe that this would be disproportionate, with a strong economic impact on our markets (DIY, professional) and for our society. TiO2 is an essential building block in paint formulations, and without it the sector would be unable to function in a proper and responsible manner. Nowadays to our knowledge there are no substitute enabling maintain the current level of performance.				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France		BehalfOfAnOrganisation	191
Comment received				
Our company is one of the foremost producers of speciality dry mix and acrylic finishes for the building industry. We have been using TiO2 as a pigment for more than 30 years in powder form for the production of dry mix renders, grouts and ready to use tile adhesives (paste).				

We use the same process in our plants to handle all additives in powder form: operators wear a protective anti dust mask FFP2, safety goggles and gloves.
Each working station is equipped with a dust aspiration. TiO2 is weighed manually before introduction into the mix of powder or paste.

To our knowledge we are not aware of any relationship between the handling by operators of TiO2 and any occurrence of cancer in the past 30 years.

TiO2 is a key raw material used in the production of our products because of its unique properties: it brings whiteness and increase the color intensity of the others pigments. This brightness and whiteness cannot be replaced by any other additives or white fillers.

The classification of TiO2 as carcinogen category 1B would result in the non-availability of aesthetic renders, grouts and tile adhesive pastes to consumers including thermal insulation systems (in relation to REACH annex XVII entry 28). This would impact dramatically the commercial activity of the whole building construction industry.

To our understanding, the main hazard could result from dust inhalation of an ultrafine powder. Therefore we would strongly recommend to follow the same safety rules than for ultrafine non crystalline powder materials such as pyrogenic or precipitated silicas.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom	Aerospace and Defence industries of Europe (ASD)	BehalfOfAnOrganisation	192

Comment received
ASD notes that harmonised classification should be based on scientific evidence, which only points at possible cancers caused by inhalation of very fine powder or nano- forms of titanium dioxide. On this basis it is our view that a Carc 1B classification be limited to only inhalable fine/nano- forms of TiO2, and not all titanium dioxide forms.
Dossier Submitter's Response
See point 1 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Spain	TOLSA S.A.	BehalfOfAnOrganisation	193

Comment received
TiO2 is a common accessory mineral in rocks and soils. It can also be found in different industrial minerals which may contain up to 3%. Clay minerals are one of the industrial minerals which may also contain TiO2. TOLSA has been supplying products based in clay minerals for different consumer and industrial markets for more than 50 years. TOLSA supplies ca. 700,000 tons of clay-based products per year for the European market. No adverse health effects have ever been reported due to exposure to these products, irrespective of the TiO2 content.

Classification of TiO2 as a carcinogen 1B would imply that probably a significant percentage of clay minerals would have to be classified because of the presence of >0.1% of TiO2 as a natural accessory mineral. This would have a massive economic impact not only in our company but also in other clay mineral producers, and in the industrial mineral sector in general, since TiO2 is a common accessory mineral in many industrial minerals. Furthermore, TiO2 is also a usual component in soils. Classification of TiO2 according to the proposal would mean that in many cases dug up soil would have to be classified, or managed as a hazardous waste.

TiO2 has been used in many consumer and industrial products for decades without any health issue for manufacturers, users or consumers. Taking into account the massive economic impact of the classification of TiO2, and the long record of continued and safe use of TiO2, any change in the classification of TiO2 should be used on solid and sound scientific evidence.

In our opinion, the CLH dossier fails to provide this evidence. We fully support the comments provided by IMA Europe, TDMA and TDIC. In particular, we consider that the CLH dossier disregards the strong evidence of the epidemiological studies, covering over 24.000 workers, and it bases its proposal on a very limited number of animal studies whose results cannot be considered reliable as to their relevance for human carcinogenic hazard.

We believe that the scientific evidence included in the CLH dossier does not support a change in the TiO2 classification, and that a more thorough, comprehensive and sound evaluation of the scientific evidence on TiO2 should be carried out.

Dossier Submitter's Response
See points 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Finland		BehalfOfAnOrganisation	194
Comment received				
I represent a downstream user / formulator of paints. We are very concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. The safety of our workers is very important issue for us, and we do our best to avoid any dust in the working air. We have been using the raw-material at least 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. As TiO2 is one of the key raw-materials of any consumer, professional or industrial paint, we are worried that the classification would also affect to our products. As the health hazard is related to the inhalation of dust, the downstream legislation due to this new classification is not justified. All finished liquid products (and all materials where TiO2 is bound to a matrix) based on the TiO2 would be affected by this new classification. The proposed classification would remove the white (and light color) decorative products from the consumer market, and make it more difficult for the professionals and industry to use paints, and thus have high economic impact to our market and to our company. The market today demands for white paints and good hiding power, and in this respect TiO2 is unique – there is no direct replacement for TiO2 with similar technical properties.				

Dossier Submitter's Response
See points 1 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Japan	KOSE CORPORATION	BehalfOfAnOrganisation	195
Comment received				
We have great concerns on negative implications for cosmetic industry caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter in sunscreen products cannot be used in the market. TiO2 has been placed in the market for more than 90 years, and the causal relation of the carcinogenicity associated with TiO2 has not been reported. If TiO2 is classified as Carc. Cat 1B-H350i by the CLP regulation, TiO2 cannot be virtually used in cosmetics. Thus, we would like to request the authorities to reconsider the classification of TiO2.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Japan		BehalfOfAnOrganisation	196
Comment received				
Impact of a CMR IB classification on cosmetic products We have great concerns on negative implications for cosmetic industry caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter in sunscreen products cannot be put in use in market. Based upon the reasons mentioned in the specific comments, we concerned about the sentence: "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B-H350i", is lack of sound scientific evidence. (4.1.6, page 69) When IARC classified TiO2 in the Group 2B "possibly carcinogenic to humans", it didn't have any negative impact on cosmetic industry since IARC does not limit the use of TiO2 as cosmetic ingredients. However, if TiO2 is classified as Carc. Cat 1B-H350i by CLP regulation, TiO2 cannot be used in cosmetics according to Article 15 of the Cosmetics Regulation 1223/2009, "the use in cosmetic products of substances classified as CMR substances (substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity), of category 1A or 1B under Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures. Though such substances may be used in cosmetic products by way of exception where all of the conditions addressed in the article are fulfilled, none of substances have been exempted by fulfilling them all to date. Thus, we would like to request the authorities to reconsider the classification of TiO2 based on more realistic exposure simulation since we believe TiO2 does not show carcinogenic potential under normal and foreseeable misuse conditions of cosmetics containing TiO2.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Japan	KANEBO cosmetics INC.	BehalfOfAnOrganisation	197
Comment received				
Impact of a CMR IB classification on cosmetic products We have great concerns on negative implications for cosmetic industry caused by the classification of TiO2 as Carc. Cat 1B-H350i since a major UV filter in sunscreen products cannot be put in use in market. Based upon the reasons mentioned in the specific comments, we concerned about the sentence: "TiO2 should be considered as being potentially carcinogenic to humans when inhaled and thus be classified Carc. Cat 1B-H350i", is lack of sound scientific evidence. (4.1.6, page 69) When IARC classified TiO2 in the Group 2B "possibly carcinogenic to humans", it didn't have any negative impact on cosmetic industry since IARC does not limit the use of TiO2 as cosmetic ingredients. However, if TiO2 is classified as Carc. Cat 1B-H350i by CLP regulation, TiO2 cannot be used in cosmetics according to Article 15 of the Cosmetics Regulation 1223/2009, "the use in cosmetic products of substances classified as CMR substances (substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity), of category 1A or 1B under Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures. Though such substances may be used in cosmetic products by way of exception where all of the conditions addressed in the article are fulfilled, none of substances have been exempted by fulfilling them all to date. Thus, we would like to request the authorities to reconsider the classification of TiO2 based on more realistic exposure simulation since we believe TiO2 does not show carcinogenic potential under normal and foreseeable misuse conditions of cosmetics containing TiO2.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Spain		Individual	198
Comment received				
We have been distributing Titanium Dioxide since more than 35 years to several industrial sectors such as paper, coatings, plastics, rubber... without any health nor safety issue ever arising or being commented. The classification of TiO2 as carcinogenic would have a deep impact not only in our business but also in our customers' companies, as there is no suitable substitute available. Furthermore this classification of TiO2 would lead to classify ALL poorly soluble powders into same carcinogenic class, which would have a massive and devastating effect on the chemical sector in EU. Frankly speaking, it appears to me like trying to classify coffee as carcinogenic just because if you drink it too hot, it may cause to you injuries that could lead to the development of throat cancer... TiO2 has been proved by many years of use to be a safe product and therefore it is not understandable the proposed carcinogenic classification.				

Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom	Rust-Oleum & Mathys	BehalfOfAnOrganisation	199
Comment received				
ECHA note - Only a non confidential attachment was submitted. Titanium Dioxide RustOleum Mathys.zip				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom	Tor Coatings & Watco	BehalfOfAnOrganisation	200
Comment received				
ECHA note - Only a non confidential attachment was submitted. Titanium Dioxide Tor Watco.zip				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom		BehalfOfAnOrganisation	201
Comment received				
The company I represent is a US owned concern but has manufacturing sites in various EU Member States (including UK, Sweden, Poland, Italy, Germany, France & Spain). We are a formulator of coatings both for the consumer and industrial markets. We are extremely concerned about the proposed classification of TiO2 as a carcinogen. Our manufacturing sites are all very well established sites, most of which have been in operation for well over 30 years and all use titanium dioxide in the formulation of products. In this time we have no incidents of workplace cancer on record linked to the inhalation of TiO2 dust. The handling and use of TiO2 and other dust producing powders is strictly controlled and successfully managed. Self contained dust booths with extraction are used for the handling and dispensing of all powders and all mixing vessels are fitted with extraction and as an added precaution all operatives wear air fed respirators. It is also of great concern to us that whilst the health concern is related to the inhalation of dust, the hazard-based approach taken by European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach, would result in all finished liquid products based on TiO2 becoming affected by this new classification. As TiO2 is a major component of many of our products it has many key functionalities				

and technical advantages including:
High refractive index, high hiding power, which allows the manufacture of fully opaque coating systems. High brightness level, delivering whites which meet the expectations of end users.
High tinting strength. Ease of processing - Titanium Dioxide is relatively easy to process and does not generally require the use of specialised milling equipment. It has a low oil absorption value, which allows paints to maintain good flow and levelling properties even when used at high levels. In addition, the low oil absorption allows the formulation of high gloss finishes. It is inert, and is compatible with most polymer systems within the paint industry. It has unrivalled UV light and weathering resistance and is used to formulate highly durable exterior coatings.

There are no direct replacements for TiO2 and an inability to use TiO2 in consumer goods would result in lower quality, lower performance coatings which fail to meet consumer expectations, this would be extremely damaging on several levels:

Manufacturers would face reduced product range/offer, reduced manufacturing volumes, reduced sales volumes, reduced revenues, reduced profits, reduced workforce requirements, etc. Consumers would be unable to purchase and use good quality EU produced white, off-white and pastel shade paints (by far the most popular choices today) for the decoration and protection of their property, as the adoption of this proposition would prohibit the use of TiO2 in consumer products. Lower quality/lower performance paints result in the need for more frequent painting, the need for more coats to deliver hiding & durability, therefore increasing costs to the consumer and potentially negatively impacting the environment.

Industrial paints would be subject to additional measures both in relation to worker safety and product labelling , and legislatively pressure (through REACH and / or the Carcinogen & Mutagens Directive) to replace TiO2 in all our products, hence leading to lower performance and adverse impacts both economically and environmentally due to more frequent application of industrial coatings.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Belgium		BehalfOfAnOrganisation	202

Comment received

I represent a paint producing company and respond on behalf of that company. We are concerned about the proposal to classify TiO2 as a carcinogen.
We formulate and produce architectural paints for the professional painter and the general public. TiO2 is a key product to manufacture white and light colored paints. We strongly believe that the proposed classification of TiO2 would have a severe and disproportionate huge economic impact to our market. The health concern on which the proposed classification of TiO2 is based, is related to the inhalation of dust. Because the approach towards regulating the use of chemical substances is hazard-based instead of risk-based, the classification of all liquid TiO2 containing paints, although there is no risk of dust inhalation for these products, would be affected in such a way that this leads to a complete ban of architectural white and light colored paints for the use by the general public. There are no other raw materials available that can replace TiO2 in paints.

Our company currently employs 260 people. We have been using TiO2 for more than 30 years. We successfully manage the workplace exposure to dust by taking the following risk management measures :
All the installations where dust producing products like TiO2 are used, are equipped with local exhaust ventilation. These installations are part of a maintenance program and the efficiency is monitored by quarterly measurements. Housekeeping procedures are implemented to wet clean the area where dust producing products are handled. The paint makers wear filtering masks FFP3 when they are handling products with dust hazard. According the specifications, at least 99% of the airborne particles are filtered. All employees who are exposed to products with dust hazard, like TiO2, take part in a health monitoring program. Once a year their pulmonary function is measured by spirometry and once every 3 years, a chest radiography is taken. This monitoring program is in place for more than 15 years and until now, there is no indication at all that the exposure to TiO2 causes loss of pulmonary function or cancer.

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Italy	Fratelli Zucchini S.P.A.	BehalfOfAnOrganisation	203

Comment received

I'm writing on behalf of the company Fratelli Zucchini S.P.A. established in Italy, a EU Member State Italy. We are formulator of adhesives and sealants, and are very concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 48 people.
We have been using this substance for more than 25 years, and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.
Obviously we've adopted all measures for a successfully control regarding exposures of dust in the workplace (Countermeasures against dust exposure are already mandatory).
TiO2 is a key material to manufacture our products, for matching the colour of the substrates onto which the product has adhered. Alternatives have not the same tinting and hiding power.
We've read the proposed classification is based only on some poor and old tests based only on rats exposed to high concentration of dust; such situation doesn't happen in real situation; in addition, mice and hamsters didn't show those effects. There aren't any evidence on humans, also after so many years TiO2 has been used.
If such a classification should be approved, also liquid, solid and pasty mixtures will be affected and will classified also without any possibility to be dangerous, not being in the form of powder; that sounds absurd.
We strongly believe that consequences would be very disproportionate as would have high economic impact to our market (sealant for building, shipbuilding industry, railway industry and automotive; professionals and industrials uses) and to our company' (in absence of equivalent substances it will be almost impossible to continue production without a worsening of the conditions of sale, production, labeling and legislative pressure). That could lead to cessation of entire production lines (because the new classification could not match the requirement of our market) and sectors (especially "Do it yourself" in white paints and sealants).

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Poland		BehalfOfAnOrganisation	204
Comment received				
I represent a downstream user / formulator of paints. We are very concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. The safety of our workers is very important issue for us, and we do our best to avoid any dust in the working air. We have been using the raw-material at least 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. As TiO2 is one of the key raw-materials of any consumer, professional or industrial paint, the classification would also affect to our products. As the health hazard is related to the inhalation of dust, the downstream legislation due to this new classification is not justified. All finished liquid products (and all materials where TiO2 is bound to a matrix) based on the TiO2 would be affected by this new classification. The proposed classification would remove the white decorative products from the consumer market, and make it more difficult for the professionals and industry to use paints, and thus have high economic impact to our market and to our company. The market today demands for white paints and good hiding power, and in this respect TiO2 is unique – there is no direct replacement for TiO2 with similar technical properties.				
Dossier Submitter's Response				
See points 1 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Marabu GmbH & Co. KG	BehalfOfAnOrganisation	205
Comment received				
I represent the company Marabu GmbH & Co. KG established in Germany and respond on behalf of that company. We are a formulator of screen, pad and digital printing inks and creative colours and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 500 people. We have been using this substance for at least 50 years, and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers during this time. The workplace exposure of dust is minimized by using big bags, supported by local exhaust ventilation. As in Germany there is a workplace exposure limit for dust in general, also measurements have been done to proof compliance, resulting in proofing that the required limit value is complied with permanently and safely. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy. Although the supposed carcinogenic properties of the product are related to dust inhalation, a classification as Carc. Cat, 1B will result in the same classification of all our products containing TiO2, despite the fact that our inks and colours are liquid and				

thus no dust inhalation of the TiO2 contained can occur. This problem results from the hazard-based classification requirements of CLP regulation not taking into account whether there is indeed a risk. About 70% of our turn-over are achieved with products containing TiO2 as white pigment. From the technical point of view, there is no alternative white pigment providing similar technical properties. Concerning our creative colours which are solely sold to the general public, classification of the colours containing TiO2 as carcinogenic will result in those shades being no longer available for private end users at all (REACH Annex XVII, section 28 restriction). Concerning the printing inks, especially screen and pad printing need high opacity usually achieved by the use of TiO2. Classification of TiO2 resp. of white and also high opaque coloured shades as carcinogenic would result in very restrictive handling and use conditions. This may result in close-down of print shops not willing or able to invest in the related equipment. Printed products then will be manufactured outside the EU, which may lead to printing ink manufacturers also moving outside EU to be closer to the customers. Some kind of products (for example toys) will be no longer allowed to be printed with white or high-opaque inks as use of carcinogenic substances in toys is prohibited by toys directive 2009/48, again resulting in loss of business and finally in loss of workplaces.
Dossier Submitter's Response
See points 1 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Landshuter Lackfabrik	BehalfOfAnOrganisation	206
Comment received				
I represent the company Landshuter Lackfabrik established in Germany and the EU and respond on behalf of that company. We are a formulator of industrial paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 70 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	International Association of Color Manufacturers	BehalfOfAnOrganisation	207
Comment received				
ECHA note - Only a non confidential attachment was submitted. ANSES_Proposal_ IACM_Comments_July2016.pdf				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Belgium	IGI - The Global Wallcoverings Association	BehalfOfAnOrganisation	208

Comment received
IGI – The Global Wallcoverings Association, represents the wallcovering industry worldwide. Titanium Dioxide is an important raw material for wallcoverings as both a pigment and an opacifier, giving wallcoverings good "hiding power" to cover wall imperfections. We have no alternative that matches its performance. There are no known cases of workers in our industry or consumers handling our products suffering ill effects from the presence of titanium dioxide in our products, yet if it is classified as a category 1B carcinogen, this could preclude wallcovering installation by consumers. Titanium dioxide is bound into the matrix of the wallcovering layers so does not represent a dust hazard to consumers. As wallcoverings are essentially a "do-it-yourself" home decoration product, we believe that this hazard classification would devastate our industry causing many of our member companies in Europe to cease operations. We support the scientific proposal put forward by the Titanium Dioxide Manufacturers Association.
Dossier Submitter's Response
See points 1, 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Romania	SC DRUCKFARBEN ROMANIA SRL	BehalfOfAnOrganisation	209

Comment received
Dear Sirs, We represent the company Druckfarben Romania S.R.L. . established in the EU Member State Romania and respond on behalf of such company. We are producers of masonry paints and printing inks and we are much concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 98 people. We have been using Titanium Dioxide for almost 10 (ten) years. The personnel in our production premises undergoes regular pulmonary examinations and no respiratory cancer symptoms have ever been referred, while a corporate doctor evaluates the relevant examination results. Therefore, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. Our company is certified with ISO 18001 and we successfully control the workplace dust exposure. Several measurements have been performed in the production to control the concentration level of the airborne particles.

Furthermore, TiO2 is a key raw material to manufacture our products. The proposed classification of the single component would also affect the classification of the chemical mixture and we expect this would have high economic impact to our market and to our company. The reason is that in such case only professional users will be allowed to handle and use the new products, whereas the do-it-your-self users, being a large market share of our production, will not be permitted to have access to these materials.

Moreover, according to the European Printing Ink Association exclusion policy, the use of any carcinogenic raw material intended to be used in food packaging is prohibited. Therefore, the application of any white (based on titanium dioxide) printing ink shall not be possible at all.

We should also stress the fact that calcium carbonate (precipitated or grounded), zinc oxide and zinc sulfide have been evaluated for substitution of titanium dioxide. However, the results were negative.

Additionally, titanium dioxide, due to the exceptional light scattering and high reflective index, is used in the production of masonry paints and printing inks to provide the following properties to the final products: hiding power, coverage, whiteness and opacity. The above properties of titanium dioxide could NOT be substituted by alternative raw material one to one.

Finally, from toxicological point of view, titanium dioxide (CAs No: 13463-67-7, PM Ref No: 93440):

1. Is a dual use additive (E-171) according to Commission regulation (EU) NO 231/2012, laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council;
2. Has a high SML (specific migration limit) 60 mg/Kg according to Commission regulation (EU) No 10/2011, on plastic materials and articles intended to come into contact with food;
3. Is included as an evaluated substance (Sml: 60 mg/kg) in Swiss ordinance of the FDHA on articles and materials, annex 6; and
4. Is an approved food color according to EFSA Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form.

ECHA note – A non confidential attachment was submitted with the comment above.
ECHA letter.pdf

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom	British Coatings Federation	BehalfOfAnOrganisation	210
Comment received				
Comments made below are on behalf of the wallcovering members of the British Coatings Federation and represent our members' views.				

ECHA note – A non confidential attachment was submitted with the comment above. Titanium dioxide comments July 16.docx
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France		Individual	211
Comment received				
I represent the company "Produits Mauler" established in the EU Member State and I respond on behalf of that company. We are a formulator of coatings (decorative paints, varnishes and woodstains) and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs fifteen people. We have been using this substance for more than twenty years. As we successfully manage the workplace exposures of dust (use of efficient ventilation and extraction and wear dust mask), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (all finished liquid products based on TiO2 would be affected by this new classification) and to our company (there is no direct replacement for this substance in coatings). The perceived impact if the French proposal is supported could include mention of the resultant ban on the sale of all decorative wall paints and white DIY products to the general public. 40% of our products contain titanium dioxide. If the French proposal is accepted and requires labeling liquid products, our company may then close.				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom		Individual	212
Comment received				
As a pathological toxicologist, I have researched and published widely on the safety of metals in biological systems. My recent publication, The Carcinogenicity of Metals: human risk through occupational and environmental exposure (Royal Society of Chemistry, Cambridge, 2014, pp429), provides a comprehensive review of the carcinogenicity of thirty eight metal and metalloid elements, several of which have been subject to contentious views on their classification. Titanium dioxide has also proved divisive in its proposed classification. My authoritative view states that "Evidence that TiO2 may be carcinogenic in humans derives largely from in vitro tests and animal trials.				

Increased cancer-related mortality was not observed in epidemiological studies and causes of death were as expected for population trends, lifestyle, smoking and exposure to other contaminants." I concluded then as now, that "chronic inhalation and intra-tracheal administration in rats has to be viewed with great caution". Secondly, the "so-called cystic keratinising squamous pulmonary carcinomas reported in rats seem to be peculiar to certain strains and are not listed in the histological typing of human lung tumours by the World Health Organisation (Geneva, 1981)". Available information provides no evidence that TiO2 is catabolised within the human lung or that it invokes any of the normal detoxification mechanisms or metabolising enzymes expressed by metabolically competent cells for bioactivation of xenobiotic materials (Castell et al, 2005; Scheuch et al 2006).

The French CLH Report for a Proposal for Harmonised Classification and Labelling dated May 2016 identifies TiO2 as being potentially carcinogenic in humans following chronic inhalation and proposes a classification as Carc. 1B – H350i. This classification is based upon supposed "conclusive and sufficient evidence" provided by inhalation or intra-tracheal administration in rats in an "overload context". Presently, there is no scientifically valid evidence that any of the isoforms of TiO2 are carcinogenic in humans, mice or hamsters.

TiO2 is insoluble in water but binds certain human serum proteins. It is absorbed phagocytically by cultured human cell lines, and macrophages which form an endogenous protective function. Eleven epidemiological communications and human case studies conducted in Europe or N.America since 1986 have failed to confirm a statistically valid relationship between occupational exposure to nanoparticulate TiO2 (PEL 15mg.m3) and lung or other cancers (Boffetta et al, 2001, 2004; Chen & Fayerweather, 1988; Ellis et al, 2010; Garabrant et al, 1987; Hext et al 2005; Keller, et al, 1995; Liao et al, 2008; Parkes, 1977; Yamadori et al, 1986; Chang et al, 2013).

I also emphasize, that current international legislation controlling scientific procedures in live animals requires veterinary guidance on the stress factors, monitoring of the relevance of the test to be conducted, and a justification of the experiment in the light of existing knowledge. The experimental protocols to implicate TiO2 as a carcinogen are considered to be inconsistent with present-day legislation on scientific procedures in live animals. Practical and ethical considerations arising from administration of substances by inhalation and intra-tracheal administration are considerable (Turner et al, 2011). The procedures used can be conducive to excessive non-specific stress-related effects.

Underlined references not included in French Proposal for CLH

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Yoshiura, Y, Izumi, H., Oyabu, T. et al, (2015) J. Nanopart. Res., 17, 241.
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ECHA note – A non confidential attachment was submitted with the comment above.
Comments on CLH proposal from A Lansdown.pdf

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

Specific response on references linked to human data:

Garabrant *et al.,* 1987, Moran *et al*., 1991 and Keller *et al*., 1995 are not clearly described in the CLH report but are included in the statement page 38 of the CLH report since these human cases are already summarized in the IARC monograph: "Other case reports were summarized in IARC monograph vol. 93 and NIOSH Current Intelligence Bulletin (CIB) 63. None of these case reports provided quantitative industrial hygiene information about workers' TiO2 dust exposure. Deposits of titanium dioxide in lung tissue as well as in lymph nodes were found. Non-neoplastic respiratory effects were observed in workers, including decline in lung function, pleural disease with plaques and pleural thickening and mild fibrosis changes. More severe reactions were observed in a few cases. However, the workers in these studies were also exposed to asbestos and/or silica."

Parkes *et al.* (1977) and Liao *et al*. (2008) do not assess the potential link between TiO_2 and carcinogenicity. Although they might inform on the plausibility of human exposure, they have many limitations and would not change the proposal. Thus, it was not deemed necessary to include them in the CLH report.

Ellis *et al.* (2010 & 2013) publications are taken into account in the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Eurocolor	BehalfOfAnOrganisation	213

Comment received

Please refer to attachment

ECHA note – A non confidential attachment was submitted with the comment above.
Eurocolour input CLH Titanium dioxide_20160712.pdf

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Verband der Mineralfarbenindustrie e.V.	BehalfOfAnOrganisation	214
Comment received				
Please refer to attachment ECHA note – A non confidential attachment was submitted with the comment above. VdMi input CLH Titanium dioxide_20160712.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany		BehalfOfAnOrganisation	215
Comment received				
We are a formulator of pigments using titanium dioxide as raw material for our products. The company <confidential> is established in the EU Member State of Germany. It looks back to a 110 years history and experience in manufacturing powder pigment preparations. I respond on behalf of that company and we are deeply concerned about the proposal made by France (ANSES) for classifying titanium dioxide as a carcinogen. We have been using titanium dioxide in powder form for decades by successfully managing the workplace exposures of dust through permanent measures e. g. housings, controlled air exchange and appropriate personal protective equipment. Based on decades of years of experience using titanium dioxide we are not aware of any relation to the development of cancer by our workers. We have a steady contact to the German "Berufsgenossenschaft" (BG RCI) where health topics in our production environment are discussed. There has never been found any health risk deriving from titanium dioxide and no statistical data give any indication in this direction. This is why we think that our handling practice is safe. It is not suitable to overestimate animal studies to a realistic and practical long term experience. Titanium dioxide is a key material to manufacture our products. The proposed classification would also affect all chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our titanium dioxide containing pigment preparations have to face a direct or indirect loss in sales either through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Greece	Druckfarben Hellas S.A.	BehalfOfAnOrganisation	216

Comment received

We represent the company Druckfarben Hellas S.A. established in the EU Member State Greece and respond on behalf of such company. We are producers of mansory paints and printing inks and we are much concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 194 people. We have been using Titanium Dioxide for more than thirty (30) years.

The personnel in our production premises undergoes regular pulmonary examinations and no respiratory cancer symptoms have ever been referred, while a corporate doctor evaluates the relevant examination results. Therefore, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.

Our company is certified with ISO 18001 and we successfully control the workplace dust exposure. Several measurements have been performed in the production to control the concentration level of the airborne particles.

Furthermore, TiO2 is a key raw material to manufacture our products. The proposed classification of the single component would also affect the classification of the chemical mixture and we expect this would have high economic impact to our market and to our company. The reason is that in such case only professional users will be allowed to handle and use the new products, whereas the do-it-your-self users, being a large market share of our production, will not be permitted to have access to these materials.

Moreover, according to the European Printing Ink Association exclusion policy, the use of any carcinogenic raw material intended to be used in food packaging is prohibited. Therefore, the application of any white (based on titanium dioxide) printing ink shall not be possible at all.

We should also stress the fact that calcium carbonate (precipitated or grounded), zinc oxide and zinc sulfide have been evaluated for substitution of titanium dioxide. However, the results were negative.

Additionally, titanium dioxide, due to the exceptional light scattering and high reflective index, is used in the production of masonry paints and printing inks to provide the following properties to the final products: hiding power, coverage, whiteness and opacity. The above properties of titanium dioxide could NOT be substituted by alternative raw material one to one.

Finally, from toxicological point of view, titanium dioxide (CAs No: 13463-67-7, PM Ref No: 93440):

1. Is a dual use additive (E-171) according to Commission regulation (EU) NO 231/2012, laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council;
2. Has a high SML (specific migration limit) 60 mg/Kg according to Commission regulation (EU) No 10/2011, on plastic materials and articles intended to come into contact with food;
3. Is included as an evaluated substance (Sml: 60 mg/kg) in Swiss ordinance of the FDHA

on articles and materials, annex 6; and 4. Is an approved food color according to EFSA Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form. ECHA note – A non confidential attachment was submitted with the comment above. Letter DF Titanium Dioxide 11 07 2016.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	REHAU AG + Co.	BehalfOfAnOrganisation	217
Comment received				
Health effects overloading the lung with fine particles or nanoparticles are known from many inert substances. Substances like TiO2 which are not intended to be sold to the general public as a powder cannot cause a risk in the general public. In the huge range of TiO2 use in consumer goods it is always enclosed in a polymeric matrix. An exposure to TiO2 in powder form in appreciable amounts is impossible. The safety provisions for workers in working areas with exposure to TiO2 dust is considered as most important. The introduction of different protection levels, for example for nano-particles with high anatase content on the one hand and for rutile standard grades on the other hand seems to be reasonable. We fully agree with the statements and scientific studies of TDIC and TDMA. The classification of a very safe substance as a carcinogen must be understood as a bureaucratic/eurocratic act and not as a protective measure for the population. The impact of TiO2 to our business is very important. More than 50 % of our production contain up to 10 % of TiO2. More than 1 Billion € of our turnover are affected by the use of TiO2. There exists no technical feasible and no commercially available alternative to TiO2. TiO2 improves the weather resistance of most polymeric resins and it has extreme importance on the lifetime of products like paints or plastic products. The socio-economic effect of a possible ban of TiO2 should be investigated considering all the costs for production and the additional consumption of raw materials and the disposal of products with missing weather resistance. All UV-radiation-energy which is transformed to heat by TiO2 today must be considered as a cause of material deterioration in a world without TiO2.				
Dossier Submitter's Response				
See points 1, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany	Verband der Chemischen Industrie e.V. (VCI)	BehalfOfAnOrganisation	218

Comment received

VCI Statement on the Proposal for a Harmonised Classification of Titanium dioxide

From the toxicological perspective, the submitted proposal for classification and labelling of titanium dioxide is neither justified nor appropriate. Therefore, no classification should be made.

Already now, existing legislation provides adequate safety. A classification would not contribute to improving the protection of health and environment, while it would have serious and disproportionately problematic effects in almost all legal fields.

In many sets of legislation – e.g. on industrial plant safety and environmental or consumer protection or special legislations on biocidal products or cosmetics – classification and labelling trigger comprehensive obligations and bans or restrictions, automatically and without any further examination of whether the use of the sub-stance really poses risks. For example, mixtures (like titanium dioxide-containing white wall paint) could be no longer placed on the market for private end consumers.

Because of the outstanding properties of titanium dioxide regarding health, safety, environment and performance, no suitable alternatives are available. Titanium dioxide already substitutes earlier used, e.g. heavy metal-containing, pigments. As the carcinogenic effect in animal testing is not substance-specific but characteristic of dusts, this can be expected to occur with all potential alternative substances too.

Because of its outstanding properties, titanium dioxide is an all-rounder raw material in almost all sectors of industry. This substance is widely used, mainly as white pigment and particularly in paints, coatings, plastics, textiles, foods and feedstuffs, in paper production as well as in pharmaceutical and cosmetic products. A classification as "potentially carcinogenic to humans" would have considerable negative impacts on entire value chains.

In the future, for all substances additional risk and impact assessments should be carried out as soon as a harmonised classification is possibly upcoming. Where sufficient risk management is already in place in uses for consumers, for workers and environment, exemptions should be granted – in accordance with proportionality – in or by those legislations that refer to the new harmonised classification. This would ensure that the legislations, which refer to classification and labelling, do not result in automatic and disproportionate restrictions or bans.

Manufacturers, importers and users should be actively involved in the examination of the risk and in impact assessments of classification proposals.

Classification decisions on substances with risk management in place should be suspended until legislations that refer to such classification are adapted accordingly.

(for further details see attached documents - in English and German)

ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI.7z

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria	Association of the Austrian Chemical Industrie	BehalfOfAnOrganisation	219

Comment received

Titanium dioxide (TiO2) is a natural mineral which is used commercially in countless applications over the past 100 hundred years. For many ten thousands workers worldwide contact with TiO2 is daily routine, and billions of consumers are exposed to TiO2.

The Austrian Chemical Industry uses approximately 15 000 tons of TiO2 per year.

TiO2 is the most important white pigment worldwide. It has light scattering, UV light absorbing and photolytic properties. Its application spectrum reaches from coatings, paints, paper, plastics, rubber, pharmaceuticals, cosmetics, coated fabrics, textiles, cosmetics, catalysts, to even food colorants. Due to the photolytic properties TiO2 enables self-cleaning surfaces and consequently reduces workplace and household accidents.

Due to is widespread use, the enormous volumes that are produced and processed, and the fact, that presumably each and every inhabitant of the earth came and come in contact with this natural mineral, it is highly unlikely, that carcinogenic properties have not been identified earlier. Since the introduction of TiO2 no such adverse health effects have been linked to workers or consumers.

A classification of TiO2 as carcinogenic would not contribute to improving the protection of health and environment, while it would have serious and disproportionately problematic effects in almost all legal fields. Due to the automatism of EU chemicals legislation, and certain EU product legislation a classification of TiO2 as CMR category 1 substance triggers automatic consequences.

The Titanium Dioxide Manufacturer Association TDMA has performed a Life Cycle Analyses, which clearly demonstrate the sustainability of TiO2, e.g. resulting from energy efficiency in reflective coatings and "cool roofs", resource efficiency with durable construction materials and waste reduction with light weight packaging films. In this respect TiO2 is an important contribution to the UN Sustainable Development Goals (SDG)

We recommend carrying out additional risk and impact assessment for TiO2.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria	GL Pharma	BehalfOfAnOrganisation	220
Comment received				
TiO2 has been used for nearly 100 years as a white pigment. Cases of exposure based health effects have not been observed. A Change to other pigments will be very costly for the pharmaceutical industry, and will be a severe disadvantage over non EU pharmaceutical suppliers. Our industry is skilled in the handling of highly toxic substances and we see us - even if there was a risk to TiO2 use - well equipped to continued use of TiO2				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Belgium	Fenzi belgium	BehalfOfAnOrganisation	221
Comment received				
I represent the company Fenzi Belgium established in the EU Member State Belgium and respond on behalf of that company.We are formulators of mirror paints, decorative paints for glass and building component paints and are concerned about the proposal made by France for classifying titanium doixyde as carcinogen.Our company currently employs more than 100 people.We have been using this substance for more than 10 years (as Fenzi, >20 years as AKZO NOBEL before...). As we successfully manage the workplace exposures of dust(refer to aspect2 detailed in page 1), we are not aware of any relation betwen the use of TiO2 and the development of cancer by our workers.TiO2 is a key material to manufacture our product. The proposed classification would also affect chemical mixtures and we strongly believe that this would be disproportionate as it would have high economic impact to our market and to our company.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria		BehalfOfAnOrganisation	222
Comment received				
Die von „ANSES" vorgeschlagene Einstufung von TiO2 (CAS:13463-67-7) als H350i (kann beim Einatmen Krebs erzeugen) ist aus Sicht der Fa. <confidential>, aufgrund folgender Fakten nicht begründet! 1- Titandioxid (TiO2) ist als Rohstoff bei <confidential> seit weit über 50 Jahren in Verwendung, ohne Anzeichen von Gesundheitsproblemen bei Mitarbeitern oder Kunden. Die lückenlose Verwendung von wirksamen Absaugungen und persönlicher Schutzausrüstung im Umgang mit TiO2 (und anderen staubenden Stoffen) führt bereits jetzt zu sicherem Umgang mit TiO2. 2- Derzeit werden bei <confidential> ca.600 Tonnen TiO2 pro Jahr verarbeitet.				

TiO2 ist in ca. 50% der Farben und Lacke (Mischungen) in relevanten Mengen (x>0,1%) enthalten. Es ist kein gleichwertiger technischen Ersatz zur Substitution von TiO2 bekannt. Durch die Einstufung „H350i" werden Marktanteile verloren gehen. Wahrscheinlich wird das zum Verlust von Arbeitsplätzen führen! 3- TiO2 ist bei Farben und Lacken in eine Harzmatrix eingebettet und deshalb nicht inhalativ verfügbar. 4- TiO2 wird in sehr vielen Bereichen eingesetzt. Es handelt sich als Weißpigment um den wichtigsten Rohstoff im Bereich Farben und Lacke! Sowohl in der „pharmazeutischen Industrie" als auch als „Lebensmittelzusatzstoff" ist TiO2 zugelassen.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		Individual	223
Comment received				
Cantillana compagny established in France, member state of the EU, being formulator and producer of various products for the building we are concerned by the proposal made by the France classified as carcinogenic TiO2.Our company employment currently 250 people. We use this substance since 1980. Ensuring the management of exhibitions successfully dust in workplace(see appearance2 page 1)we are not aware of a relationship between the use of TiO2 and the development of cancer in our workers.TiO2is a fisrt key in the manufacture of our products. The proposed classification would also affect chemical mixtures and we firmly believe that this would be disproportionate,whit a strong economic impacton our market and our society. A part of our business depends on TiO2 and to date no raw material replacement exists, we are thereby legetimize worried about the sustainability of some our formulations in terms of jobs and economic consequences				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		BehalfOfAnOrganisation	224
Comment received				
The replacement of TiO2 is difficult because TiO2 provides the highest wet opacity for wallpapers made of paper or nonwoven materials. There are no other chemical additives providing similar properties. Covering and masking behavior of wallcoverings in wet state of wallcoverings during				

processing will be worse and even in dry state there would be a considerable difference in opacity which may result in customers dissatisfaction.
Dossier Submitter's Response
See point 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United Kingdom	MANOR COATING SYSTEMS LIMITED	BehalfOfAnOrganisation	225
Comment received				
We manufacture paints for industrial, professional and consumer use directly employing around 80 people in the UK. Titanium Dioxide is a key component in many of the products we manufacture and sell. We draw your attention to: There is no direct replacement in paint -We have used Titanium Dioxide in our business for over 40 years and have no reported incidents of cancer -When loading Titanium Dioxide we do so under controlled conditions which include the use of loading system, extraction and PPE -When supplied to the consumer the material is in a resin matrix not a dust form We believe that the proposed classification is disproportionate, not supported by practical evidence and would have a huge economic impact throughout the EU.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	France		BehalfOfAnOrganisation	226
Comment received				
Our Company is downstream user and importer of Titanium Dioxide for cosmetic industry. Titanium Dioxide, nano or not, is widely used in cosmetic industry, in powder form or not, for colorant or UV-filter fonction. TiO2 represents a huge part of our Company production and sales. Our Company workers use TiO2 powder on a daily basis since 1976 and no case of cancer have been declared among them. This classification as CMR1B by inhalation put many industries and companies at risk, Titanium Dioxide being present everywhere! Every foundation powder uses Titanium Dioxide, so all women/men having a foundation powder is exposed to inhalation of Titanium Dioxide on a daily basis. Classifying TiO2 as CMR 1B by inhalation would mean that a huge portion of the population is at risk, and all people having lung cancer would now sue the brand of their foundation powder...!?!				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	France		BehalfOfAnOrganisation	227
Comment received				
I represent the company <confidential> established in the EU Member State and respond on behalf of that company. We are a formulator of paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 36 people. We have been using this substance for 54 years. As we successfully manage the workplace exposures of dust (refer to aspect 2 detailed in page 1), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public, refer to aspect 3, detailed in page 1) and to our company' (refer to aspect 4, detailed in page 1).				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Belgium		BehalfOfAnOrganisation	228
Comment received				
I represent a printing ink manufacturer located in Belgium and respond on behalf of that company. We are a formulator of printing inks (UV offset and flexo, so paste or liquid inks) and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 110 people. We have been using this substance for more than 20 years. As we successfully manage the workplace exposures of dust (by using ventilation,dust extraction and proper Personal Protection equipment), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers over a long periode (the last 20 years). TiO2 is a key material to manufacture our printing inks . We have used last 20 years more the 1000 tons of TiO2 (last years 60 tons per year). The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public) and to our company. The health concern is related to the inhalation of dust, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach, all finished liquid products, like our inks, based on TiO2 would be affected by this new classification. We are using TiO2 in all our opaque white inks. Opaque white is a necessity when you want to print on transparent materials. Without opaque white you can not print clear images on transparent substrate, that are more and more used in the packaging industry. TiO2 gives very good opacity and there is no direct replacement for this substance in inks with the same characteristics. The perceived impact if the French proposal is supported could include the resultant ban on the sale of all white printing inks products to the general public, the introduction of additional measures related to worker safety and				

product labelling , and legislatively pressure (through REACH and / or the Carcinogen & Mutagens Directive) to replace TiO2 in all our opaque white printing inks.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		BehalfOfAnOrganisation	229
Comment received				
I represent the company <confidential> established in Germany and respond on behalf of that company. We are a formulator of printing inks, wallpaper coatings, functional coatings, ahesives, and waterproofing systems and markings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 278 people. TiO2 is a key material to manufacture a lot of our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		BehalfOfAnOrganisation	230
Comment received				
I represent the company <confidential> established in Germany and respond on behalf of that company. We are a formulator of paints and coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 90 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Italy		BehalfOfAnOrganisation	231
Comment received				
'I represent the company <confidential> established in the EU Member State ITALY and respond on behalf of that company. We are a formulator of PAINTS and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 150 people. We have been using this substance for 55 years. As we successfully manage the workplace exposures of dust (WE MANAGE TiO2 IN A				

CLOSED SYSTEM), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market and to our company. THERE ISN'T A VALIDE SUBSTITUTE TO TITANIUM DIOXIDE.
Dossier Submitter's Response
See points 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		Individual	232
Comment received				
Dear Sirs, I represent the company Zeller&Gmelin GmbH&Co KG established in the 1866 in Germany and respond on behalf of that company. We are a formulator of printing inks and coatings and are concerned about the proposal made by France for classifying Titaniumdioxide - TiO2 -as a carcinogen – CMR 1B. Our company currently employs around 160 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy. We have been using this substance for at least 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled. TiO2 is of very high relevance to my company Zeller+Gmelin GmbH&Co KG. It is used in printing inks, coatings and lacquers such as primers, varnishes, topcoats for metal, plastic and paper substrates. White printing inks are used in food- and non-food applications (food packaging materials. The percentage of TiO2 in our products is typically between 20% and 50 %. TiO2 containing products are usually printed with an ink lay down of around 5g/m² for Flexo printing and 25 g/m² for Screen printing. The key functionality of TiO2 is the extremely high hiding power resulting in a very good opacity. Furthermore the Whiteness and UV resistance (hardly any Yellowing) plus the chemical resistance of TiO2 is unbeatable. Furthermore we have to enhance that the industry is depending on the following characteristics of TiO2: TiO2 is used with a high grade of purity meaning the level of residues is down to zero. TiO2 is inert and therefore causing no side reactions with components of the ink or coating. For the industry the ease of particle size control, incorporation in the formulation, the long-term and thermal stability makes TiO2 very important for the coatings and printing ink industry.				

A substitution of TiO2 with the same final properties is not possible. Substitutes with reduced resistance properties and have already been restricted due to higher hazards.

German producers of printing inks and coatings do export world-wide meaning they had to compete with TiO2 containing products of the Non-EU producers which would be a clear disadvantage and would result in market loss.

The proposed reclassification has severe existence threatening implications for us as a manufacturer of printing inks and coatings plus our share of the printing ink and coating market. Job losses are therefore highly probable.

A 1:1 substitution of TiO2 with the same final properties of formulations is not possible. The development of TiO2 free products would be affected by a significant burden on H&S measures and would have worse properties leading to a clear competitive disadvantage compared top Non-European manufactures.

With best regards

<confidential>

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
10.07.2016	United Kingdom	Zircon Industry Association (ZIA)	BehalfOfAnOrganisation	233

Comment received

1. The classification ignores the overwhelming evidence that TiO2 does not cause cancer in humans and by applying the mode of action it is quite clear the data in rats is not relevant for humans for all such poorly soluble particles. There are numerous references in the literature that review this mode of action
2. There are very many inconsistent statements and assumptions made without due explanation or evidence and in addition conclusions made without following CLP guidelines.
3. The ZIA supports the specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA) and the Titanium Dioxide Industry Consortium (TDIC). (Note the ZIA, includes mining companies producing feedstock raw materials for TiO2 pigment production, i.e. ilmenite, rutile, synthetic rutile and TiO2 slag)

Dossier Submitter's Response
See point 2 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Austria		Individual	234
Comment received				
There is no proper replacement for TiO2 in paints. Known alternatives are of lesser qualitity and even more poisonous.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Austria		BehalfOfAnOrganisation	235
Comment received				
Titanium dioxide is widely used as the standard white pigment in many paint systems, because of the excellent combination of its properties: high refractive index leading to high colour strength and hiding power, low hardness which makes it easy to grind to the ideal particle size due and easy to disperse in the organic binders of the paint, absence of acute or chronic toxicity effects. Additionally, Titanium dioxide pigments are inert against water and allow the formulation of stable waterborne white paint formulations, whereas other white pigments tend to react with water leading to discolouration or decay of the paint before use. This unique combination of properties of titanium dioxide, especially in its Rutil structure, made it replace all older white pigments in most product groups. Potential replacements of Titanium dioxide suffer from severe drawbacks: - Zinc oxide (lower refractive index which means less color strength, classified for aquatic toxicity: H410), tendency to react with water and some binder systems - Barium sulfate (much lower refractive index meaning much less color strength, high hardness which makes it extremely difficult to grind and disperse): can only be used as a filler to increase density of a coating, not as a real pigment to define its colour - Lithopone and Zinc sulfide (lower refractive index i.e. less color strength, less light-fastness): Zinc sulfide shows high tendency to degrade under UV irradiation which leads to darkening and yellowing of the coating film. Therefore, Lithopone and Zinc Sulfide cannot be used in high-quality topcoats for outdoor application and cannot replace titanium dioxide in such outdoor applications. The stabilization of Zinc Sulfide by doping with inorganic Cobalt salts is known, but these inorganic Cobalt salts have shown carcinogenic effects in animal studies and have therefore been classified for carcinogenicity cat. 1B, too. Colour and hiding power are caused by light scattering at small particles of high refractive index. In order to achieve equal performance in the coating, potential replacements have to have similar particle size as Titanium dioxide. So, any potential replacement of Titanium dioxide as a pigment would naturally be also a powder-like material with low particle size, i.e. in the same range as Titanium dioxide. If the proposed carcinogenic effect of Titanium dioxide is not substance specific, but is caused by inhalation of large quantities of small particles that lead to inflammation of the lung tissue, any replacement can be anticipated to have a similar effect like Titanium dioxide under the same conditions of the study. Our company uses several tens of tons per year of Titanium dioxide pigments for almost seven decades in order to manufacture white and coloured pigment pastes. During this period no cases of lung cancer related to the handling of Titanium dioxide were observed in the workers. This is in line with epidemiologic studies; even the CLH report refers to				

this fact on page 8:
"Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. […]"
The carcinogenic effect of Titanium dioxide proposed in the CLH report is linked to the inhalation of Titanium dioxide dusts. This type of exposure to aerosols normally only occurs in workplaces. As dust exposure limits exist in various national Safety and Occupational Health regulations, legal means to minimize this kind of exposure are already in place and implemented in all industries using Titanium dioxide. Workers in our company e.g. wear dust filter masks as a minimum, or even positive-pressure full-face respiratory protection masks, when they handle pigments like Titanium dioxide or other dusty materials. The consequent use of such personal protection equipment eliminates the risk of being exposed to dusts. The proposed classification as carcinogen cat 1B would not improve the level of protection per se, thus.
The conclusion of our company is that the proposed classification of Titanium dioxide as a carcinogen cat. 1B would lead to a complete phase-out of Titanium dioxide from a central type of goods in everyone's daily life, while suitable replacements have drawbacks in terms of performance and also partially in terms of hazards. The socio-economic cost of a phase-out of Titanium dioxide will be high, as nearly all products of daily life are coated or coloured, whereas there is no real improvement of the protection level to be anticipated.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	United Kingdom	The British Adhesives and Sealants Association	BehalfOfAnOrganisation	236

Comment received
BASA represents over 100 adhesive and sealant businesses in the UK and Ireland, the majority of whom are SMEs. Almost all our members provide products that contain TiO2 that will be adversely affected by the suggested reclassification. We do not know of any suitable alternative material.
Dossier Submitter's Response
See point 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Denmark		BehalfOfAnOrganisation	237

Comment received
I represent the company – Downstream user – established in the EU Member State Denmark and respond on behalf of that company. We are a formulator of liquid printing inks for sausage casings, flexible packaging and paper (decoration) and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 45 people. We have been using this substance for 60 years. We successfully manage the workplace exposures of dust by the use of efficient

ventilation when handling any material, which may be considered a dust hazard. We are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. We use approximately 200 tons TiO2 annually. 70 – 80 % of our products contain TiO2. The proposed classification would affect our chemical mixtures, i.e. all finished liquid products based on TiO2 would be affected by this new classification and we strongly believe that this would be highly disproportionate to the danger, as the health concern is related to the inhalation of dust – not other forms. It would have high economic impact to our market (especially in casings printing and lamination inks). Printing on casings or packaging using TiO2 is likely to be banned completely. There is no direct replacement for this TiO2 in our inks, so classification of TiO2 (in all forms) could have the consequence that we would have to reduce our company drastically or close entirely. We also expect that the impact on our many customers company's would be drastic – with a high loss of jobs.
Dossier Submitter's Response
See points 1, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany	Paul Jaeger GmbH & Co KG	BehalfOfAnOrganisation	238
Comment received				
We are a producer of paint specialties for buildings. Most of our products are in white colour so the use of titanium dioxide as a white pigment is essential for us. About 90% of our turnover depends on products based on titanium dioxide. Our company's history as a small medium sized company lasts now for more than 100 years. We are very concerned about the proposal because there is no adequate replacement for titanium dioxide as a pigment in white paints and coatings. Titanium dioxide is widely used also in cosmetics and food and legalized for this use. As a consequence if titanium dioxide would be kept with the corresponding labelling it would lead to confusion among the consumers. Paints with alternative pigments would miss the high technical standard of today's products.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Switzerland		BehalfOfAnOrganisation	239
Comment received				
<confidential> represents app. 60 companies producing paints, inks and varnishes in Switzerland and selling them within Switzerland and into the EU. We respond on behalf our member companies to the public consultation about the proposal made by France for classifying titanium dioxide as a carcinogen. Our member companies have been using titanium dioxide safely for decades. As the companies successfully manage the workplace exposures of dust (e.g. efficient ventilation and extraction and other risk management measures), we are not aware of any relation between the use of TiO2 and the development of cancer by workers. There were no cases of cancer in the workforce caused by the inhalation of TiO2 during the manufacture of coatings or inks over the last 30 years in Switzerland. The health concern of the French				

proposal is related to the inhalation of dust, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach. From the toxicological perspective, a classification of titanium dioxide as potentially carcinogenic is neither necessary nor justified. There is no evidence of a carcinogenic effect in humans. In epidemiological studies no connection was found between the exposure at the workplace and a cancer risk. TiO2 is a key material to manufacture products as paints, coatings and printing inks. Moreover all finished liquid products based on TiO2 would be affected by this new classification. This would result in a ban on the sale of all decorative wall paints and white DIY products to the general public, the introduction of additional measures related to worker safety and product labelling, and legislatively pressure to replace TiO2 in all products. At this stage there is no direct replacement for TiO2 in coatings and inks. Raw materials for replacement (e.g. zinc oxide and zinc sulphide) can be of inferior quality and critical in ecological and toxicological terms, especially if they contain heavy metals. In addition, dust exposure is also expected in the processing of alternative substances. Therefore the coating and ink industry would face a severe problem when the use of TiO2 would be restricted. The reclassification of TiO2 would have serious negative effects on the market for paints, coatings and printing inks without contributing to the protection of health and the environment.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany	Ostchem Germany GmbH as OR	BehalfOfAnOrganisation	240
Comment received				
AS OR of a NON-EU Manufacturer we like to add following information: Conforming to Ukrainian legislation, all our personnel is subjected to regular annual medical inspections and investigations during all their employment at the company, at medical institution attached to the company. Titanium dioxide manufacture operates starting from 1963. Statistics on professional diseases at titanium dioxide manufacturing plant is maintained in term of 53 years and witnesses the lack of respiratory organs oncological diseases increased level in the given production, compared with other productions. The level of oncological diseases in our personnel does not exceed the level of such diseases throughout the whole country. The given observations enable to conclude that titanium dioxide dust does not have carcinogenic impact on human lungs.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Belgium		BehalfOfAnOrganisation	241
Comment received				
• Titanium dioxide is used as a pigment in a large majority of rubber closures of pharmaceutical packaging systems and diagnostics systems (like blood collection				

stoppers).
• In these applications it is an inert material and has no negative effects on the compatibility of the rubber closures and the drug.
• It would be extremely difficult to replace titanium dioxide. Eliminating titanium dioxide would cause huge cosmetic problems and unstable color for many pharmaceutical rubber formulations. It would not be possible to find an inert alternative to replace it.
• Elimination or replacing titanium dioxide in all these formulations would also have a huge impact on the whole pharma industry because all registrations where these closures are involved, would need to be reviewed (including new stability studies because the formulations have changed). The impact of this would be hard to imagine.

Dossier Submitter's Response
See point 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Greece	NEOKEM S.A.	BehalfOfAnOrganisation	242

Comment received

• 'I represent the company NEOKEM SA established in Greece and respond on behalf of that company. We are a formulator of Powder Coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen.
• TiO2 is a key material to manufacture our products,95% of our formulations contain 1-33% of Tio2. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public, and to our company', especially when it is well known that Tio2 is the only technically reliable white pigment.So there is no other solution to produce white and off white colors.

Dossier Submitter's Response
See point 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Greece	Vitex - Hermes Yannidis Bros S.A.	BehalfOfAnOrganisation	243

Comment received

Our company currently employs 230 people. We have been using TiO2 for 55 years. As we successfully manage the workplace exposures of dust with efficient ventilation and appropriate masks for our workers to wear when they handle TiO2 in powder form or any other powder we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.

TiO2 is a key material to manufacture our products and is used in over 85% of our products. There is no alternative that offers the same characteristics and advantages to our products, such as whiteness, opacity, brightness, protection from UV light, stability and durability. It is the best way to provide an opaque white or colored layer for decoration and protection for walls, metal objects, wooden trim and furniture, plastic films, and other substrates.

Although the classification proposal is for TiO2 as inhalable dust, it would affect liquid and paste-like products even though it is not available for exposure by inhalation from our products. Also, acceptance of this classification might lead to similar actions regarding the use of other powders.

We strongly believe that this would be disproportionate as it would have high economic impact to our market. Products containing TiO2 would not be permitted for sale to the general public, and there will be need for special controls for professional and industrial users. Also proposed classification would have high economic impact to our company as it would lead to significant loss of business and might ultimately also lead to loss of many jobs.

Moreover, classification that may lead to making paint applicable by professionals only will render the simple redecoration of a room very expensive and practically impossible to low income individuals and families who would like to DIY (do it yourself) thus downgrading their standard of living.

* We fully support the position provided by TDIC and TDMA, which is NO labeling of TiO2.

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Sweden		BehalfOfAnOrganisation	244
Comment received				
The TiO2 in our products is bound in polymer in a fixed film and would never be released as dust in a user Environment. I strongly believe that this is the case in allmost all applications where TiO2 is used in consumer Products.				
Dossier Submitter's Response				
See point 1 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Hungary		Individual	245
Comment received				
I'm a miniature painter who uses all kinds of paints. This ban just doesn't make any sense - all kind of dust inhaled have this effect, and what this'd only achieve is to make paint manufacturers either go out of business as Titanium Dioxide is the base of many paints that cannot be replaced in any way, or change their formulas which could also lead to going out of business. Millions use Titanium Dioxide based paints, and we're doing alright, no need to regulate this.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Denmark		BehalfOfAnOrganisation	246

Comment received

Introduction of TiO2 in 1920s made huge improvement in white paints. It gives better whiteness, better hiding power, and better gloss resistance of paints. It substituted white lead and zinc oxide. The technical advantages are elaborated as below:
• Optical properties of white pigments such as hiding power (ability to hide the substrate) and lightening are predominately due to light scattering.
• Titanium Dioxide pigments have the greatest light scattering power of all white pigments.
• If white pigments with inferior optical properties were used, it would result in more paint layers or thicker films being required to give the same coverage of the substrate.
• TiO2 provides protection from UV damage by absorbing UV rays that would degrade the organic binder.
• Inferior pigments would provide less protection of exterior substrates leading to increased maintenance requirements and the associated costs.
• TiO2 is not only used in white shades, but also other shades as well and whilst perhaps being less critical in the darker shades, will nonetheless give the same issues as above for paler shades.
• Our workers are trained to use personal protective equipment (dust masks) as standard procedures in our factories and in our laboratories, when handling any material that may be considered a dust hazard.

To the best of our knowledge we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public).

Our customers are via our Safety Data Sheets informed about using the proper personal protective equipment when using our products. The risk of inhaling TiO2 when using liquid paints is not existing, the risk of inhaling solvents is much higher. We believe that a more exposure-based approach should be used, instead of taken the hazard-based approach, if the latter approach is used all finished liquid products based on TiO2 will be affected by this new classification.
• If white paints disappear from the market, it will result in higher consumption of electricity due to the darker colour at home/office.

• It will ban the sale of paints containing TiO2 to the general public.

• For the professional user and consumer, this would lead to significant increases in time and labour costs. There will also be an economic impact for public sector.
• There would be increased consumption of resources in terms of the other raw materials, packaging etc.
• Inferior pigments would provide less protection of exterior substrates leading to increased maintenance requirements and the associated costs.

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Germany		BehalfOfAnOrganisation	247
Comment received				
Our comany is a producer of paints, plasters, coatings and related products, with >5.000 employees and a turnover of > 1 billion €. TiO2 is the most important white pigment by far and is part of almost all pigmented formulations. We use TiO2 since more than 60 years and have not received any indication about health related problems with TiO2, neither from our employees, nor from our customers. The proposed classification for TiO2 as a carcinogen does not seem to be justified, as some findings in the CLH report clearly point out that there is no evidence that TiO2 would induce cancer in humans. Furthermore it seems to be quite clear that the finding in test with rodents are not specific for TiO2 but a result of a "lung overload", which would be similar with any other insoluble fine powder. Efficient exhaust ventilation and/or personal protection equipment is always applied when any fine powder - not only TiO2 - is handled in production sites. All relevant OEL are met (as there is no specific OEL assigned for TiO2 in Germany, the "General Dust" values are applicable: 10 mg/1,25 mg for inhalable/respirable dust). The proposed classification would cause the obligation to substitute TiO2. However, there isn´t any other white pigment that even begins to compare with TiO regarding opacity, durability, brightness. And there is no other white pigment - which would be also an inorganic powder - with proven lower hazards than TiO2. Thus the replacement of TiO2 could even result in reduction of worker´s safety, as substances might be used for which no comparable long term experience and extensive toxicological knowledge are available. The claimed health risk is related to inhalation only. However, the hazard-based approach in European regulations for chemicals would probably result in consequences also for liquid mixtures containing TiO2, although there isn´t any inhalation risk. The proposed classification for TiO2 would severely affect our business. Products containing TiO2 would face restrictions for sales to general public. And products containing TiO2 substitutes would suffer from considerably reduced technical performance, which will not be accepted by our customers.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Belgium		BehalfOfAnOrganisation	248
Comment received				
TiO2 has been used within our manufacturing organization and we believe that good industrial hygiene practices can control potential occupational exposures to inorganic dust particles. Once incorporated into the polymer matrix, TiO2 is considered to be encapsulated and no migration of TiO2 out of the polymer matrix has been observed to date. We also believe that it is known that inorganic dust particles can pose a potential concern				

for inhalation. TiO2, as such, could pose a similar concern, but as indicated earlier, exposure can be controlled by good industrial hygiene practices.
Dossier Submitter's Response
See points 1, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Germany	FIDE-Federation of the European Dental Industry	BehalfOfAnOrganisation	249

Comment received

Members of FIDE are manufacturers particularly of medical devices. Several medical devices contain titanium dioxide as pigment in bound form (e.g. in several plastic parts which are components of medical equipment). Additional titanium dioxide is used in many materials, which are used in the dental field e.g. as filling materials, impression materials or luting cements. In all of these uses titanium dioxide is present in a bound form being practically not released from the product neither for inhalation nor for other exposure scenarios. Titanium dioxide is a pigment that is hardly exchangeable. Any using of alternative substances would result in a considerable impairment of function and/ or aesthetics. On the one side this would work against the requests of the patients, on the other side the ban of titanium dioxide would be compensated by a considerable higher part of other pigments with suboptimal characteristics of function and toxicology. Furthermore certain applications of modern technology (scanning of impressions in the digital workflow of manufacturing of indirect restorations) would be more difficult or no longer possible.

We think the submitted proposal for classification and labelling of titanium dioxide is inappropriate from the toxicological perspective. Therefore, no classification as carcinogenic category 1B should be made.

Titanium dioxide has been used safely for many decades. No increased incidence of lung cancer has been observed. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. All relevant guidance documents by ECHA, OECD or the ECETOC Report unanimously observe that the results from "lung overload" studies in rats (used in the proposal as basic studies for classification) should not be transferred to humans for several reasons.

Titanium dioxide has significant positive characteristics regarding health, safety and environment. There are no suitable alternatives. Titanium dioxide already substitutes earlier used, e.g. heavy metal containing pigments. As the carcinogenic effect in animal testing is not substance-specific but characteristic of dusts, this can be expected to occur with all potential alternative substances too. Titanium dioxide is widely used, mainly as white pigment and particularly in paints, coatings, plastics, textiles, foods and feedstuffs, in paper production as well as in pharmaceutical and cosmetic products or medical devices. A classification as "potentially carcinogenic to humans" would have considerable negative impacts on entire value chains.

The existing legislation provides adequate safety. In many directives or regulations exist obligations, bans or restrictions whether the use of the substance really poses risks. In these cases manufacturers are obligated to undertake measures of classification and labelling. Examples are the "REACH" regulation (Annex VI-CMR substances; Annex XVII, point 28-30 –restriction of CMR-substances in consumer products), EU Waste Framework Directive, Biocidal Product Regulation, Cosmetics Products Regulation or the Medical Device Directive, 2007/47/EC-amending 93/42/EEC. In the introducing reason No. 29 of this directive is mentioned that "in accordance with the essential requirements on the

design and manufacture of medical devices, manufacturers should avoid the use of substances that may possibly compromise the health of patients, in particular of substances which are carcinogenic, mutagenic or toxic to reproduction, and should, as appropriate, strive to develop alternative substances or products with a lower risk potential". Additional Annex I (essential Requirements) No. 7.5 of directive 93/42/EEC regulates that „ the devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.
If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates. If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures".

The new Medical Device Regulation, which will be set into force at the end of 2016, specifies and extends these requirements. From this follows that manufacturers will have additional efforts although the use of titanium dioxide in a bound manner in dental medical devices does not lead to an unjustifiable risk.

Therefore we are convinced that a classification would not contribute to improving the protection of health and environment as well as the existing regulations and requirements are sufficiently.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Germany	EWIMA: European Writing Instruments Manufacturers Association	BehalfOfAnOrganisation	250

Comment received

Addressing CLH report: 2. "Manufacture and uses", 2.2 "Identified uses"

EWIMA members manufacture products for professional and graphic use as well as consumer's use. TiO2 is used in paints (e.g. finger paints, school tempera paints, hobby & art paints), lacquers & coatings for pens, printing inks, cores of colored pencils, crayons, artist chalks or pastels, modelling clays, erasers, correction materials, but also in plastic materials, fibres and as photocatalyst.

Concentration of TiO2 in finished products range from 3-35% in pencils and similar products, up to 50% in artist´s chalks, pastels or similar products, up to 47% in correction fluids and about 1% in erasers.

The key function of TiO2 in products of the writing instruments industry is the bright whiteness. It is used in many different materials for several functions, e.g. as white pigment, for coloration support (to allow the dyes of the formula to be fixed, necessary to develop a wide range of colors). TiO2 is a powerful pigment opacifying, protects inorganic pigments from light (TiO2 capture the radiation) and a strong UV protector.
The technical advantages of TiO2 are highest opacity, highest white color power, highest processability, highest dispersibility, high purity, high definition of particle size and a good availability.

There are no equivalent alternative materials addressing the same technical function. No other material provides anything near the bright whiteness, covering and stability within the specifications provided by TiO2, necessary for products of the writing instruments industry.
Other known materials would be ZnO, Lithopone (BaSO4 and ZnS) and "White lead" (2PbCO3·Pb(OH)2). Not only that the technical performances in all parameters are worse than TiO2 but also the toxicological profile of "White lead" is of high concern.
Additionally, about 17 elements e.g. Barium, Lead or Zinc are restricted to certain migration limits in the European legislation on toy safety. Consequently, this strict migration limits have to be applied to products of the writing instruments industry considered as toys.
In colored pencils, white Kaolin could replace a limited proportion of TiO2 but TiO2 can't be substituted at 100%. Alternatives to replace TiO2 in correction fluids are known but it results in highly reduced covering properties. The substitution will impact the technical performances of the products and TiO2 can't be substituted at 100%.
At this time, the EWIMA members have no knowledge on industrial solutions regarding the substitution of TiO2 in erasers and on correction tapes.

Addressing CLH report 4.1.6 "Conclusions on classification and labelling"

Proposition 65 requires the State of California (US) to maintain and update a list of chemicals known to the state to cause cancer or reproductive toxicity. TiO2 is listed on Proposition 65, but only as airborne, unbound particles of respirable size (airborne particles = 10 microns or less in diameter).
The risk of cancer is associated with inhalation of these particles. A similar unspecific risk is known from any small respirable particles, including those found in air pollution, which can cause cancer due to their ability to deeply penetrate into the lungs.

Once TiO2 is dispersed in e.g. a liquid ink or is bound in other matrices, it is no longer respirable. Consequently, a classification of a respective mixture or material is not justified.

We are convinced that consumer products containing TiO2 are safe and do not bear a health risk which originates from the pigment.

The proposed classification of TiO2 as carcinogenic is scientifically not justified and thus has to be dismissed (see specific comments).

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Austria		Individual	251
Comment received				
TiO2 is used in pharmaceutical production of film coated tablets, Primary and secondary packaging.The described potntial risks apply solely to TiO2 dusts. Standard respiatory Equipment can effectively safeguard against this hazard. A reformulation to a-less studied- alternate White Pigment is extremely costly and detrimental to our competitiveness.				
Dossier Submitter's Response				
See points 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	United Kingdom		BehalfOfAnOrganisation	252
Comment received				

Dear Sirs

We view with great concern the decision by the French Agency for food, Environmental and Occupation Health & Safety (ANSES) to submit a proposal to the Chemicals Agency (ECHA) for TiO2 to be classified as a Category 1B carcinogen by inhalation.

We are a small to medium sized company who manufacture a wide range of products which contain Titanium dioxide for UK and export markets. The substance is formulated to produce principally PVC plastisols for the wall covering industry, though it also finds use in a variety of adhesives, synthetic and natural latex based products.
We consider Titanium dioxide to be unique in providing the properties required in the finished product, these include-

- Whiteness
- Opacity
- Consistency
- UV stability

We do not consider their to be any alternatives on the market which are as efficient and can perform the same functions in the finished product as TiO2. Indeed some alternatives may present other hazards which make them difficult to consider for use.

We have been using TiO2 for many years, and have not had any instances amongst our workers, or customers of reported illnesses due to the use of Tio2, or the use of articles containing TiO2. Indeed the company ensures that all the necessary risk management measures are in place when operators are handling all powders including TiO2.These include wearing PPE (gloves /safety glasses/dust masks/overalls) and suitable extracting is available when TiO2 is added to mixing vessels.

VLP use in excess of 40 tonnes of TiO2/annum. Loss of TiO2 could have significant

implications for VLP, putting at risk up to 1800tonnes of business. This could have serious consequences for our presence in the markets involved. This could also have serious effects on the profitability of the company and employment prospects of staff employed by VLP. VLP believe that the proposal could have major economic implications for industry and consumers. The cost of alternative products and technologies will in all likelihood be greater, consumers will struggle to meet the increased costs associated with the new products and technologies there would also be the associated knock on effects to industry and workers.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Netherlands		BehalfOfAnOrganisation	253
Comment received				
Article 37(4) of Regulation (EC) No 1272/2008				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Germany	Worlée-Chemie GmbH	BehalfOfAnOrganisation	254
Comment received				
Being a Distributor for titanium dioxide for more than 40 years we have never heard of any lung cancer reported for workers. Having in Germany the General dust Limit value (ASGW) we think this is a sufficient measure to protect workers from the exposure of titanium dioxide dust or any other Mineral dust. Titanium dioxide is widely used also in our daily life. It should be made quite clear that a classification CARC Cat 1B of titanium dioxide will lead to a ban or severe restriction of titanium dioxide in many sectors, for example cosmetics, pharmaceuticals, DIY sector,plastic toys, stationary products, all kinds of Food packaging etc. We fully agree with and Support the Position of TDMA/TDIC and VCI regarding the scientific comments given.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	France	BS Coatings	BehalfOfAnOrganisation	255
Comment received				

We are a coating company employing about 100 people. As a coating formulator and manufacturer, we have used TiO2 for more than 40 years. Our production plant is equipped with safety apparatus and personal protection equipment is mandatory to avoid exposition of people to chemicals including TiO2. In more than 40 years, we never noted any relationship between the use of TiO2 and work-related illness. TiO2 is critical to our activity and the proposed classification will have a huge impact without relevant arguments: we think that deeper analyses shall be performed on TiO2 containing materials (such as our coating) before generalising such a classification. This key raw material is used for manufacturing more than 50% of our finished products and, today, there is no satisfactory technical alternative offered on the market.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	ACTEGA Terra GmbH	BehalfOfAnOrganisation	256
Comment received				
I represent the company ACTEGA GmbH established in the Germany and respond on behalf of that company. We are a formulator of Coatings and Varnishes and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 150 people. TiO2 is a relevant material to manufacture in some of our products categories. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Austria		BehalfOfAnOrganisation	257
Comment received				
The proposed classification of TiO2 as Carc. 1B, H350i is scientifically not justified for the following reasons: Human data do not suggest an association between exposure to TiO2 and the risk for cancer. Animal studies on rats were performed at high exposure to TiO2, which leads to „lung overload" effects. All relevant scientific guidelines (OECD, ECHA, ECETOC) point out, that „lung overload" studies on rats can not be extrapolated to humans. Furthermore, the observed adverse effects in the rat lung result from an inflammation process due to particle uptake. This is not a substance-specific effect.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	258
Comment received				
I represent the company <confidential> established in the EU Member State Germany and respond on behalf of that company. We are a manufacturer of coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently has 106 employees. We require a large quantity of TiO2 in our paint as this is the only white pigment available on the market which offers opacity, whiteness, UV resistance and compatibility. We have been using this substance for more than 30 years. We successfully keep the workplace free of dust (we use efficient ventilation and extraction and other risk management measures). We are not aware of any connection between the use of TiO2 and the development of cancer (no cases of cancer in our company caused by the inhalation of TiO2 during the manufacturing of coatings over the past 30 years). We believe that it is important that this is a generally dust-related statement, rather than being specifically related to TiO2 and the classification discussion. TiO2 is a key material to manufacture our products. The proposed classification would also affect the chemical mixture and we strongly believe that this would be out of proportion as it would have a high economic impact on our market (industrial and professional, none of our customers want to buy product with health classification GHS08 Category carcinogen 1B. up to 0.1% in our products) and on our company. If the classification of the TiO2 as a powder changes we must adapt the classification of the paint material. Our customers are not subject to this danger when purchasing our paint materials as the substance TiO2 is no longer in powder form as described above. This amendment does not correspond to any danger arising from the paint material. The substance TiO2 no longer exists as powder when contained in the liquid paint material. The health concern is related to the inhalation of dust, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances instead of a more pragmatic risk-based approach, all finished liquid products based on TiO2 would be affected by this new classification.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	259
Comment received				
I represent the company <confidential> established in the EU Member State Germany and respond on behalf of that company. We are a manufacturer of coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently has 81 employees. We require a large quantity of TiO2 in our paint as this is the only white pigment available on the market which offers				

opacity, whiteness, UV resistance and compatibility.
We have been using this substance for more than 30 years.

We successfully keep the workplace free of dust (we use efficient ventilation and extraction and other risk management measures). We are not aware of any connection between the use of TiO2 and the development of cancer (no cases of cancer in our company caused by the inhalation of TiO2 during the manufacturing of coatings over the past 30 years). We believe that it is important that this is a generally dust-related statement, rather than being specifically related to TiO2 and the classification discussion. TiO2 is a key material to manufacture our products. The proposed classification would also affect the chemical mixture and we strongly believe that this would be out of proportion as it would have a high economic impact on our market (industrial and professional, none of our customers want to buy product with health classification GHS08 Category carcinogen 1B. up to 0.1% in our products) and on our company. If the classification of the TiO2 as a powder changes we must adapt the classification of the paint material. Our customers are not subject to this danger when purchasing our paint materials as the substance TiO2 is no longer in powder form as described above.

This amendment does not correspond to any danger arising from the paint material. The substance TiO2 no longer exists as powder when contained in the liquid paint material. The health concern is related to the inhalation of dust, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances instead of a more pragmatic risk-based approach, all finished liquid products based on TiO2 would be affected by this new classification.

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	260

Comment received

I represent the company <confidential> established in the EU Member State Germany and respond on behalf of that company. We are a manufacturer of coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently has 388 employees. We require a large quantity of TiO2 in our paint as this is the only white pigment available on the market which offers opacity, whiteness, UV resistance and compatibility.
The substance TiO2 no longer exists as a powder in our coating materials but embedded in a polymer matrix, thus the dangers connected with this substance in powder form no longer exist. We have been using this substance for more than 50 years.

If the classification of the TiO2 as a powder changes we must adapt the classification of the paint material. All finished liquid products based on TiO2 would be affected by this new classification. This amendment does not correspond to any danger arising from the paint material. The substance TiO2 no longer exists as powder when contained in the liquid paint material. The health concern is related to the inhalation of dust, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances instead of a more pragmatic risk-based approach.

Our customers (did not wish to purchase any products with health classification GHS08 Cat. Carc. 1B.) are not subject to this danger when purchasing our paint materials as the

substance TiO2 is no longer in powder form as described above. Our customers will have to introduce additional measures related to work safety. The legislative pressure (through REACH and / or the Carcinogen & Mutagens Directive) will impose us to replace TiO2 in all our products, but there is no alternative for this substance on the market.

Furthermore, neither our Health and Safety Executive nor our company doctor have ever detected any problems with those employees working with TiO2 in powder form over the past 20 years. This has been checked on a regular basis.

At <confidential> all employees working with powder substances wear protective masks, our company uses efficient ventilation and extraction and other risk management measures. Up to now, we are not aware of any connection between the use of TiO2 and the development of cancer or any respiratory diseases or allergies after handling this substance.

Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	FeRFA - The Resin Flooring Association	BehalfOfAnOrganisation	261

Comment received
WE fully support the VCI statement which has already been submitted. ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI Statement TiO2 English.pdf
Dossier Submitter's Response
See response to VCI comment No. 218.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Dane Color UK Ltd.	BehalfOfAnOrganisation	262

Comment received
We are a manufacturer of daylight fluorescent pigments which use titanium dioxide as raw material for our products. The company Dane Color UK Ltd. is established in the EU Member State United Kingdom and I respond on behalf of that company and we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen on the basis of poor scientific information. Our company currently employs 60 people. We have been using titanium dioxide in powder form for over 60 years by successfully managing the workplace exposures of dust through permanent measures in combination with appropriate personal protective equipment. Based on this 63 years' experience of using titanium dioxide we are not aware of any relation to the development of cancer by our workers. Titanium dioxide is a key material to manufacture in some of our products. The proposed classification would affect these, other formulations in which our products are used and the absence of a high opacity white basecoat would further limit the utility of our products in coatings

applications. We strongly believe that this reclassification would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. This proposed change also affects many downstream users of our products who would have to face a direct or indirect loss in sales either through legal restrictions or changed customer behaviour. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards.

We urge a very careful review of not only the socio-economic effects but also scrutiny of the data put forward by the French ANSES/CLH which appears insufficiently robust.

<confidential>
Dane Color UK Ltd.

6th July 2016

ECHA note – A non confidential attachment was submitted with the comment above.
TDMA response 2016-07-06.docx

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	Weilburger Coatings GmbH	BehalfOfAnOrganisation	263

Comment received

I represent the company Weilburger Coatings GmbH established in Germany [EU Member State] and respond on behalf of that company. We are a formulator of industrial coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 300 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.

Dossier Submitter's Response

See point 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom		Individual	264

Comment received

I am working as a consultant in the printing ink industry. Previously I was employed by the largest printing ink company in the world, since 1977. Titanium dioxide is the only suitable pigment to obtain opaque whites at ink application weights. A company I currently work with used 19 tonne during last year to make 48 tonnes product. In all my time in the industry, which is a responsible user of health and safety equipment such as

extraction, I have never encountered, or heard of, any incidence of cancer associated with Titanium Dioxide, nor indeed any illness. I believe the proposed classification will serve no purpose except to needlessly make it more difficult to use an essential product.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	Krahn Chemie GmbH	BehalfOfAnOrganisation	265
Comment received				
I represent the company Krahn Chemie GmbH established in Germany and respond on behalf of that company. We are a distributor of speciality chemicals and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently supplies multiple small, medium, and large enterprises for which TiO2 is a key material to manufacture their products. We understand that the consequence of the proposed classification would negatively affect their production and their markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as our customer's companies and to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Netherlands	Unipro BV, member of UZIN-Utz AG	BehalfOfAnOrganisation	266
Comment received				
As a member of the UZIN-Utz group, Unipro bv (NL) is a manufacturer of Arturo resin floorings. We do use TiO2 in colouring our products. The classification proposal in the CLH report is based essentially on studies in rats exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload" effects. No increased incidence of lung cancer by humans has been observed. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. As the carcinogenic effect in animal testing is not substance-specific but charac¬teristic of dusts, this can be expected to occur with all potential alternative substances too. Titanium dioxide is an indispensable input in the formulation of resin floorings. As good as all pigmented floor coverings like resin screeds, smoothy floorings, sealants contain titanium dioxide. Because the reasons are based on huge dust exposure and no realistic translation from rats to humans, we say that the proposed classification and labelling is inappropriate and would have serious and disproportionately negative impacts for our industry.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Denmark		Individual	267
Comment received				
We are using TiO2 in our board production, in our lacquer and oil production and we are selling board, lacquers and oils to Denmark and wider world. Externally the Professional flooring people are using our Lacquers and Oils, but also the sanding process of our board then ever you need to maintenance and recoating the floor. It can be in Sports Areas, in Homes, in working places etc. So many People will be affected of either the liquid Paint/Oil and/or the dusting. We fill a big responsibility to those People using our product in one way or another, for their Health and Safety both in short and long terms. We write of course in our SDS's and Technical advises how to handle and protect you self during the use and of coarse also how to get rid of the waste. Internally, the lacquer factory we have instructed the workers to use a mask with suitable filters, wish gloves and other safeties that they are going to use, handling the Pigment and Pastes. In our board production they have the same instruction from the Health and Safety Department and the Product Development Laboratory. We have been using TiO2 in different forms since the company were founded back in 1938. The Company to have products declared after REACH and CLP restriction and we recently got the Danish Indoor Climate labelling mark. We have luckily enough not hear about one single person that had got cancer after working with Pigments and therefor had the risk of inhalation of TiO2 during the manufacture of coatings or oils, in all this years. At Junckers Industries we believe that this discussion should be a generic dust-related statement and not specifically related to TiO2 and its classification. ECHA note – A confidential attachment was submitted with the comment above. Consultation TiO2_ECHA_20160706.pdf				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany		BehalfOfAnOrganisation	268
Comment received				
We are developing and producing preparations for specific applications like paint ffor tosy-used as Toys; Food packaging. These formulations are based on high purity grades of titanium dioxide. Due the the small batch size of 100 to 1000 kg starting from pigment in paper bags. We are doing this business since more than 100 years and did no register specific effects on the health of our employes. Alternative white pigments, with lower opacity would disclose the thin layer films, which are produced by our customers.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany	Protec Systempasten GmbH	BehalfOfAnOrganisation	269
Comment received				
I represent the company PROTEC Systempasten GmbH established in the year 1995 [Herdecke; Germany] and respond on behalf of that company. We are a formulator of colorants/ pigment concentrates and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 28 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Denmark	Beck & Jørgensen A/S	BehalfOfAnOrganisation	270
Comment received				
Please see attachment ECHA note – A non confidential attachment was submitted with the comment above. Indsigelse mod klassificering af Titandioxid som kræftfremkaldende.pdf				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany		Individual	271
Comment received				
We are a manufacturer and formulator of pigments using titanium dioxide as raw material for our products. The company is established in the EU Member State Germany. I respond on behalf of that company and we are deeply concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 15 people. We have been using titanium dioxide in powder form for many years by successfully managing the workplace exposures of dust through permanent measures eg. controlled air exchange in combination with appropriate personal protective equipment. Based on this 30 years experience of using titanium dioxide we are not aware of any relation to the development of cancer by our workers. Titanium dioxide is a key material to manufacture some of our products. The proposed classification would also affect a lot of chemical mixtures and we strongly believe that this would be disproportionate as it would have highly negative economic impact to our market compared to minimal risk reduction to the consumer. Since all downstream users of our titanium dioxide products have to face a direct or indirect loss in sales either				

through legal restrictions or changed customer behavior. Many national laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when it is bound in a polymer matrix and thus not exposing any health hazards .
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	United Kingdom	British Retail Consortium	BehalfOfAnOrganisation	272
Comment received				
TiO2 has been used used in a very wide range of products over a long period of time. It is used in paints, coatings , adhesives, paper, plastics, rubber, printing inks, fabrics, textiles, catalyst systems, ceramics, floor coverings, roofing materials, cosmetics , pharmaceuticals, food colourants etc. Almost anything that is white. Impact on downstream users if classified as 1B carcinogen, would include: - Exposure controls at the workplace, - Increased hazard labelling requirements, - No EU Ecolabel claims, - Restrictions on use: Cat 1b carcinogens are restricted to professional use (REACH Annex XVII), - Restricted use in sensitive applications such as cosmetics, pharma and food ranging from a ban or obligation to substitute to potential re-evaluations, - Potential addition to textile consumer article restricted list, etc. The rat may be preferred model to gauge the potential chronic hazards of inhaled titanium dioxide, but it is untrue and inaccurate to assume that these tests equate the assessment of risks of inhaled materials to humans. Experts have questioned the relevance of the rat model. Rat lung tumours are unique to that species under certain exposure conditions. Management (CRARM) considered that it is wasteful to expend limited risk assessment resources, risk management time and public and legal involvement revisiting the issue of human relevance. The CRARM specifically identified titanium dioxide particles as one such chemical, because observed rodent tumour response associated with exposure to TiO2 particles are not relevant to human risk. (Presidential/Congressional Commission on Risk Assessment, 1997).				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	France	Pébéo	BehalfOfAnOrganisation	273
Comment received				
I represent the company Pébéo established in France and respond on behalf of that company. We are a formulator of artist colours and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently				

employs 150 people. We have been using this substance for more than 50 years. As we successfully manage the workplace exposures of dust (we use efficient ventilation and extraction and other risk management measures when handling any material that may be considered a dust hazard), we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is the only white pigment used by every artist all around the world. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market : Artist colours are sold to general public, all finished liquid products based on TiO2 would be affected by this new classification and could result on ban on the sale of 75 % of all artist colours.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany	Steelpaint GmbH	BehalfOfAnOrganisation	274
Comment received				
I represent the company Steelpaint GmbH established in Germany and respond on behalf of that company. We are a formulator of anti-corrosion paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 60 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Netherlands	Chugoku Paints BV	BehalfOfAnOrganisation	275
Comment received				
Titanium Dioxide is a key substance to the paint manufacturing industry and its downstream users. In over fifty years of use we are not aware of any negative health issues for our coworkers or our customers. On the other hand the environmental, social and economic result of the suggested classification would be immense. Many jobs would be lost in the paint manufacturing industry and the industries that use our products. On top of that there would be heat reflective paints, thus increasing the need for air conditioning of domestic and office buildings all over Europe.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Finland		MemberState	276
Comment received				
In the CLH report page 4 it is mentioned that "There is only one registration dossier (EC no 236-675-5) for "titanium dioxide" which indicates that there is sufficient data to support a mono-constituent substance under REACH of "all crystal phases & hydrates of titanium dioxide including rutile, anatase, monohydrate and dehydrate". It is further mentioned that "Based on available evidence and information in the registration dossier (e.g. mechanism of carcinogenicity, characterization of the particles), the proposed scope for the Annex VI entry is: "Titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies". The FI CA does not agree with the above-mentioned reasoning and conclusion on the proposed scope for the Annex VI entry. The CLH report (page 4) mentions that "crystal phase, morphology, lattice stabilizers or surface treatment included in the scope of this REACH registration dossier are not clearly reported". It is stated in the CLH report page 7: "In the context of dossier evaluation under REACH, a final decision has been issued by ECHA to the lead registrant with requests to transparently report the scope of the registered substance in terms of crystalline phase, morphology and surface chemistry". Therefore, as there is uncertainty of the REACH registration information in terms of substance composition and properties, the FI CA considers that the reference to the coverage of REACH registration cannot be used to support the proposed Annex VI entry. In addition, grouping of all TiO2 particles together without giving any value to their different characteristics is misleading and against the common understanding that nano-sized particles should be evaluated independently from the fine particles (Shi et al. 2013). The lack of information of particle characteristics (size, shape, crystallinity, surface area, coating, purity, etc) used in the different experiments limits the value of the data and conclusions. The IARC report does not separate nano- and micro-forms of TiO2, however the report is from 2006 and discussion on nano-issues has risen after that. Therefore this should not be used as a reasoning not to separate different forms in CLH report. The FI CA appreciates the effort of the FR CA to consider the role of physicochemical properties of TiO2 (size, crystalline phase, coating) on carcinogenicity. However, strong conclusions and generalizations based on the data used in the CLH report should not be drawn as the literature review is rather insufficient.				
Dossier Submitter's Response				
See point 1 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany	Verband TEGEWA e. V.	BehalfOfAnOrganisation	277
Comment received				
The submitted proposal for classification and labelling of titanium dioxide is inappropriate from the toxicological perspective. Therefore, no classification should be made. A classification would not contribute to improving the protection of health and environment, while it would have serious and disproportionately problematic effects in almost all legal				

fields.

Please see detailed comments with reference to the use of titanium dioxide in textile and leather manufacture in the attached pdf file.

ECHA note – A non confidential attachment was submitted with the comment above. Final_TEGEWA_TiO2.pdf

Dossier Submitter's Response

See points 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany	Verband der deutschen Lack- und Druckfarbenindustrie e. V. (VdL), the German paint and printing ink association	BehalfOfAnOrganisation	278

Comment received

From our viewpoint the proposed classification and labelling of titanium dioxide as "presumed to have cancerogenic potential for humans" is not justified from the toxicological perspective and would have serious negative impacts on the European and German markets for paints, coatings and printing inks.

The paint and printing ink industry is a major purchaser of titanium dioxide. Over 50% of titanium dioxide produced in Germany go into paints, coatings and printing inks, up to 200,000 tonnes per year. Titanium dioxide is used in many fields of paints, coatings and printing inks, e.g. in

- Decorative coatings
- Plaster and putty
- Anti-corrosion coatings
- Wood varnishes and paints
- Industrial coatings
- Printing inks
- Vehicle refinishing coatings
- Powder coatings
- Traditional organic paints
- UV-curing coatings

Depending on the formulation, the concentration of titanium dioxide ranges, on average, e.g. in decorative coatings from 15-35%, in plaster and putty up to 30%, in anti-corrosion coatings up to 20%, in vehicle refinishing coatings 25%, in traditional organic paints up to 40%, up to 50% in industrial coatings, up to 20% in wood varnishes and paints, and up to 55% in printing inks.

Titanium dioxide is extremely lightfast, has a high refractive index and a very high light scattering capacity. From the coloristic perspective it has, therefore, the highest opacity among all white pigments as well as an excellent brightening capacity vis-à-vis coloured media. Furthermore, titanium dioxide is thermally stable, not combustible, nearly insoluble in water, and weather and UV resistant.

For paints, coatings and printing inks, there are hardly any alternatives to titanium dioxide. Other raw materials (e.g. calcium carbonate, zinc oxide and zinc sulphide) are usually of inferior quality regarding stability and opacity, brightness (gloss) and abrasion resistance. Often, replacement substances are critical in ecological and toxicological terms, especially if they contain heavy metals like e.g. zinc oxide, zinc sulphide or lead carbonate. In addition, a substitution of titanium dioxide would not change the given situation since the carcinogenic effect in animal testing is not substance-specific but characteristic of dusts (see specific comments below) and dust exposure can be expected also in the processing of alternative substances.

A harmonised classification as potentially carcinogenic would have far-reaching impacts on many legal provisions (e.g. on the safety of industrial plants and environmental and consumer protection). Comprehensive obligations and bans or restrictions would be the automatic consequence, without any further examination of whether the use of titanium dioxide in real life poses any risks. For example, a classification of titanium dioxide as potentially carcinogenic according to Annex XVII points 28 and 30 of the REACH Regulation would result in a ban for the sale of paints and coatings to private final consumers (e.g. in do-it-yourself stores). Moreover, titanium dioxide would need to be substituted – irrespective of whether replacement substances of equal quality are available.

Due to the inferior quality and the higher costs of replacement substances, considerable damage to the national economy must be expected. Our member companies also fear that the discussion about titanium dioxide will cause uncertainty among customers and, consequently, lead to a reserved buying behaviour.

Under a sector goal, the companies of the German paint and coatings industry have made the commitment to generally abandon by 2020 the use of raw materials classified as carcinogenic, mutagenic and toxic to reproduction (so-called CMR substances) of categories 1A and 1B. This goal builds on a successful earlier sector initiative which reduced by two thirds the volume of CMR substances used in this sector. Regarding printing inks, already since 1995 the EuPIA exclusion policy has been applied (EuPIA = European Printing Ink Association). This policy stipulates that no CMR substances can be used in printing ink, as a standard. A classification of titanium dioxide as potentially carcinogenic would put into question this voluntary sector initiative.

Conclusion:

From the toxicological perspective, a classification of titanium dioxide as potentially carcinogenic is neither necessary nor justified (see specific comments below). Given the automatic link to regulatory requirements, such a classification would have serious negative effects on the market for paints, coatings and printing inks without contributing to the protection of health and the environment. The risks under discussion are based solely on dust exposure by inhalation. But this is not substance-specific for titanium dioxide; it is characteristic of a large number of dusts. Against this backdrop, we propose to give up plans for a classification and labelling of titanium dioxide. Instead, a new binding dust limit value could be introduced for the handling of titanium dioxide at the workplace.

At present, substances are classified at EU level exclusively on the basis of their intrinsic properties. The real risk in the use of a substance is not examined. Because of the automatic linking to classification in many legal provisions on occupational health and

safety and consumer and environmental protection, this approach can lead to excessive and unintended restrictions. The given case of titanium dioxide is an example of this. For this reason, we are advocating in favour of additional risk and impact assessments to be performed in future for all substances as soon as a harmonised classification is proposed. Verband der deutschen Lack- und Druckfarbenindustrie e. V. (VdL, the German paint and printing ink association) represented over 180 – mostly mid-sized – manufacturers of paints, coatings and printing inks vis-à-vis politicians, public authorities, other industries, science and the media. The VdL stands for over 90 percent of this industry in Germany. In 2015 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed ca. 25,000 staff. ECHA note – A non confidential attachment was submitted with the comment above. VdL-Position TiO2_30.6.2016.pdf
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99 and VCI No. 218
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		BehalfOfAnOrganisation	279
Comment received				
The potential carcinogenic of TiO2 activity has only been shown in an old study in inhalation with probably overloading the lungs of the rats. There may be a potential risk with TiO2 dust but the use of TiO2 in the final product like liquid inks, or printed packaggn materials has no any risk of dust formation. However due to the current labeling rules and also committment of EuPIA member not to use carcinogens, this would have massive impact also on our products.				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany	CD-Color GmbHCo. KG	BehalfOfAnOrganisation	280
Comment received				
I represent the company CD-Color GmbH Co. KG established 1892 in Germany and respond on behalf of that company. We are a formulator of architectural coatings, and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 165 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy. Since the formation of CD-Color GmbH KG, no case is known to us, in which the use of titanium dioxide for workers or users has caused health impairment.There are no technically equivalent alternatives to the use of titanium dioxide.Other white pigments raise, because of there content of heavy metals, toxicological concern.Titanium dioxide is				

found in many products of foods, cosmetics or detergents and cleaning agents industry application.Hereby the Intended use is often the oral ingestion or contact with the skin and these products enter drains.A rating of titanium dioxide as carc. 1b leads to a flood of Labelling of products which would be difficult for the consumer to identify real hazard. This would be a less of security and not an increase.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	France	Geholit chimie de peinture et de revêtements	BehalfOfAnOrganisation	281
Comment received				
We represent the Geholit Sarl located in the EU Member State of France and respond on behalf of that company. Our company currently employs about 30 people. As a producer of industrial and protective coatings we are concerned about the proposal made by France to classify titanium dioxyde as carcinogen. Ti02 is a key material to our products with a maximum content of about 20%. We expect negative consequences of the proposed classification affecting strongly our production and our markets. With regard to the toxicological assesment we believe that the proposal is disproportionate and would have serious negative impacts on our company as well as on the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany		Individual	282
Comment received				
I represent the Company TIGERIT-WERK, Lack- und Farbenfabrik established in Germany and respond on behalf of that Company. We are a formulator of industrial coatings for over 80 years. TiO2 is a key raw material in our products. Over 50% of our formulations contain TiO2 between 0,1-30%. The new cassification of TiO2 would have serious negative Impacts to our Company and many other industry sectors (e.g. pharmaceutics, cosmetics, Food, paper, etc.)				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Denmark	National Research Centre for the Working Environment	BehalfOfAnOrganisation	283

Comment received
1) This report represents a very nice piece of work. The report is clearly written and the conclusions are clearly argued and evidenced. The conclusion to classify Titanium Dioxide as 1B is very much in line with the classification from IARC 2) The authors describe a number of surface modifications of TiO2 in various applications. In our view, the variation of possible surface modifications are even larger than described. Furthermore, surface modifications are sometimes inadequately described by the supplier. See fx ' Inflammatory and genotoxic effects of nanoparticles designed for inclusion in paints and lacquers. Saber AT, Jensen KA, Jacobsen NR, Birkedal R, Mikkelsen L, Møller P, Loft S, Wallin H, Vogel U. Nanotoxicology. 2012 Aug;6(5):453-71. doi: 10.3109/17435390.2011.587900. Epub 2011 Jun 7. PMID: 21649461'
Dossier Submitter's Response
See point 1 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	France		BehalfOfAnOrganisation	284
Comment received				
I represent the company (SME – 200 employees) established in France, EU Member State, and I respond on behalf of this company. We are a formulator and producer of paint fillers (as defined in the European standards EN 16566) and decorative effect coatings for more than 75 years. We are much concerned about the proposed classification for TiO2 as a Carcinogen category 1B as it would impact our company Our company currently employs 200 people and provides its products and solutions to consumers and professional users over a large numbers of countries in EU. In our products, TiO2 is used from a few percent up to 10 % to provide key properties such as whiteness, opacity, colour acceptance and stability. There is no alternative material that brings similar performances. All existing alternatives so far tested provide poor quality in our products when they are not classified dangerous for the environment. In our company, we are not aware of cases of cancer due to exposure to TiO2. We do manage the risks of dust exposure at the work place by applying the precautions for safe handling (wearing a suitable respiratory protection) as we do for all powder products and raw materials. On the other hand, in our products, TiO2 is embedded in a liquid matrix. Therefore we think TiO2 is not available to cause inhalation toxicity. All the more as we recommend to our users to wear respiratory protection during the preparation and sanding phases. The proposed classification for TiO2 would also affect the classification of our products, and we do think it would have disproportionate economic impact : it would cause the non-availability of our products to consumers and a direct profit loss of more than 2 M€ per year, plus indirect loss on our organisation (10 FTE directly impacted / significant loss of employment for toll manufacturers (SME mainly)...				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Karl Wörwag Lack- und Farbenfabrik GmbH & Co. KG	BehalfOfAnOrganisation	285

Comment received

We are a producer of coatings and paints in Germany and have been operating in this business for nearly 100 years. Over decades, we have been using titanium dioxide on a large scale and up to now we have not observed any occupational disease among our workers related to the use of this substance. Moreover, titanium dioxide has a widespread use in a variety of other businesses, including food and cosmetics industry, and there has not been any relationship between human exposure to titanium dioxide and cancer in any field of application so far.

Considering the proposed harmonised classification and labelling of titanium dioxide we are very concerned because we do not see any scientific and/or epidemiologic evidence that this substance should be classified as carcinogen category 1B (inhalation).

This is substantiated by the fact that the available data on carcinogenicity from two experimental studies in rats published in the CLH report are not reliable sources for the purpose of classification of titanium dioxide as carcinogenic. From a toxicological point of view, these studies show several methodological deficiencies, including the study design, routes of application and the selection of concentrations for exposure of the test animals. Especially, the use of very high concentrations of titanium dioxide for inhalation exposure and the corresponding "lung overload" effects are not considered to be of toxicological relevance with respect to human health risk assessment.

As stated in the OECD Guidance Document on Acute Inhalation Toxicity Testing (No. 39) "[…] Insoluble materials deposited in the alveolar region of the lung may accumulate over time with resultant impairment of particle clearance and particle-mediated inflammatory response. Hence, the lung dose accumulated over time may be decisive for the outcome of the test. […]". With respect to titanium dioxide, which is a very poorly soluble substances, not its intrinsic toxicological properties are crucial for acting as a carcinogen, but rather physiological processes leading to lung deposition and subsequent tissue inflammation caused by excessive exposure to its particles. Such mechanism are not substance-specific but rather characteristic for a wide range of dusts (e.g. coal dust, hardwood dust).

Thus, classification of titanium dioxide as carcinogenic is not adequate considering its intrinsic properties and would therefore lead to a misclassification. If a majority of the material we use would be classified as carcinogenic based on titanium dioxide, it would not assist our employees in being sensitive to the real toxicological risk from other substances having the same classification. In worst case, we would achieve a general ignorance when handling substances that bear a real risk for human health.

Instead we think, it would rather make sense to regulate inhalative occupational exposure to dusts in a European harmonised approach. In Germany, exposure to dusts is already controlled by a general exposure limit of 10 mg/m³ as published in the Technical Rules for Hazardous Substances (TRGS).

As part of our responsible care, we keep a strong focus on worker safety. When handling powders and dust cannot be avoided, we have technical installations in place to reduce inhalative exposure. Combined with adequate personal protection equipment, our worker exposure is well below the national regulatory requirements mentioned above.

Thus, from the worker safety prospective and toxicological point of view, we do not agree with the proposed classification of titanium dioxide as carcinogen category 1B (inhalation).

We also see a strong socioeconomic impact of this proposed classification - not only for us but for the whole branch of industry. As titanium dioxide is one of the most frequently used pigments in our products with important technological properties, we would be

strongly affected if a wide range of products could not be marketed anymore based on this disproportionate classification. There would be the obligation to substitute this substance which is not realistic when considering the poor alternatives on the market. Consequently, a reduction in our product portfolio would lead to significant economic losses and would finally threat the employment of our workers. We appeal to the risk assessment competence of the European Chemicals Agency in critically evaluating the proposed classification and labelling of titanium dioxide by the French authorities.
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Jänecke+Schneemann Druckfarben GmbH	BehalfOfAnOrganisation	286
Comment received				
Ich vertrete und antworte im Namen von Jänecke+Schneemann Druckfarben GmbH, ansässig in Deutschland. Wir entwickeln und produzieren Druckfarben und sind besorgt über den französischen Vorschlag, Titandioxid als kanzerogen einzustufen. Zur Zeit sind bei uns 160 Mitarbeiter beschäftigt und Titandioxid ist für uns ein entscheidender und äußert wichtiger Rohstoff. Die vorgeschlagene Einstufung hätte weitreichende Konsequenzen für die Produktion und Vermarktung unserer Produkte. Im Hinblick auf die toxikologische Bewertung meinen wir, dass der Vorschlag unangemessen ist und große negative Auswirkungen sowohl für unsere Firma als auch für die gesamte Wirtschaft hätte.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Switzerland	Karl Bubenhofer AG	BehalfOfAnOrganisation	287
Comment received				
I represent the company Karl Bubenhofer AG established in the Switzerland and respond on behalf of that company. We are a formulator of paints and varnishes and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 300 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	J.W. Ostendorf GmbH	BehalfOfAnOrganisation	288
Comment received				
As one of the Major Producers of decorative paints in Europe with an installed volume of more than 500 Million Liters TiO2 is an absolute key raw material for uns and our industry and we are using it since more than 65 years. Any restriction would have massive impact on our industry, Company and the market for decorative paints - DIY as well as Professional				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		BehalfOfAnOrganisation	289
Comment received				
I represent the company <confidential> established in the Germany and respond on behalf of that company. We are a formulator of paints and varnishes and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 75 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		BehalfOfAnOrganisation	290
Comment received				
I represent the company <confidential> established in Germany and respond on behalf of that company. We are a formulator of paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 20 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		Individual	291
Comment received				
A product widely used in toothpaste, chewing-gum, sun-cream, paint, plastics etc. for decades suddenly is a dangerous chemical? A product safe for foodstuff, cosmetics etc. is a dangerous chemical?				
Dossier Submitter's Response				
See the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		Individual	292
Comment received				
I represent the company Südwest Lacke + Farben GmbH & Co. KG established in Germany and respond on behalf of that company. We are a formulator of paints and coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 120 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom		BehalfOfAnOrganisation	293
Comment received				
We make specialty paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. We employ 60 people and have used this substance for more than 50 years. We manage our factory using proper practices and protective equipment and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public) and to our company.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	France		BehalfOfAnOrganisation	294
Comment received				
I represent a paint producer established in France, the EU Member State and respond on behalf of that company. We are a formulator of paints and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 800 people. We have been using this substance for more 30 years. As we successfully manage the workplace exposures of dust, we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products. The proposed classification would also affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our market (industrial, professional and general public and more globally to our company.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	Germany	Jonas Farbenwerke GmbH & Co. KG	BehalfOfAnOrganisation	295
Comment received				
I represent the company Jonas Farbenwerke GmbH & Co. KG established in Germany [EU Member State] and respond on behalf of that company. We are a formulator of architectural coatings & render and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 73 people. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would negatively affect our production and our markets. With regard to the toxicological assessment we strongly believe that the proposal is disproportionate and would have serious negative impacts to our company as well as to the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	WUK	BehalfOfAnOrganisation	296
Comment received				
As EU Regulatory manager I am responding on behalf of a company that has factories, employing more than 200 people, in UK, Germany, France, Spain & Italy. We develop and manufacture specialist surface coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. We have been using this substance for >45 years and manage the workplace exposures of dust (aspect 2 detailed in page 1 of CLH report) and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. TiO2 is a key material to manufacture our products and there is no suitable alternative with the covering power, temperature and chemical resistance available. The proposed classification would also affect chemical				

mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our industrial and consumer markets (aspect 3, detailed in page 1) and to our company (aspect 4, detailed in page 1). Additionally TiO2 is considered food contact safe being listed in 10/2011/EU and is currently used in foods and medicines. Any restriction on its use would reduce the production of coatings in the EU and give an advantage to companies outside the EU who could export items coated with a white paint into the EU
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	Sinkro UK Limited	BehalfOfAnOrganisation	297
Comment received				
I have been involved in the Development and manufacture of printing inks for 31 years and white ink incorporating 25-60& Titanium Dioxide has been critical to the business. In the 4 ink manufacturers for whom I've worked in that period, I am not aware of any instances of any cancer caused by inhalation of Titanium Dioxide. As dust in general has long been regarded as a hazard in the manufacture of printing inks; dust protection has been available and used in the form of positive dust extraction and personal protection equipment. The concern should be dust related and not specifically Titanium Dioxide use. In addition, the effect on the printing ink manufacturing industry on restricting the use of Titanium Dioxide would be commercially disastrous as white ink is used on almost all packaging and there is no feasible, safe direct alternative. Other aspects of life would be adversely affected by any resultant ban such as Sunscreen, toothpaste, food shelf life, household paints and wall coverings. The proposed classification would have a disproportionate adverse effect on general quality of life and a severe economic impact in the coatings industry.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	HMG paints	BehalfOfAnOrganisation	298
Comment received				
Our company is HMG paints established October 1930 i.e. 86 years. Across all that time we have used Titanium Dioxide as a white pigment for our paints. We are extraordinarily concerned about the proposal made by France for classifying Titanium dioxide as a carcinogen. Our company employs 193 people and we have used this substance since our inception. We are not aware were of any linkage between titanium dioxide and workplace cancer by our workers. As you will understand operate under controlled conditions where we manage all workplace exposure to dusts and fumes. This is a necessity associated with the cleanliness required in coatings manufacturer. The proposed classification would create havoc within HMG and our industry as there are no alternatives to Titanium dioxide for the manufacture of white and pastel paints for all applications. The impact would have devastating consequences to our industry overall				

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Lithuania	UAB "Veika"	BehalfOfAnOrganisation	299
Comment received				
UAB VEIKA manufactures inks and other products for manufacturers of wallpaper and technical textile, as well as inks for digital printing since 1991. TiO2 has been used by our company for many years without any problems and in all this time we have never had information of health problems from our workers. TiO2 we use as a white pigment. If the classification is agreed upon we are facing serious problems, because there are no suitable raw materials available. This will lead to significant loss of business and might ultimately also lead to loss of jobs.				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	United Kingdom		BehalfOfAnOrganisation	300
Comment received				
We employ over 550 people globally, with 501 people employed in the EU producing, marketing and selling paint to the home decorative market. The recent proposal from ANSES to classify titanium dioxide as a carcinogen has serious and far reaching implications for us. When used as a pigment in paints, titanium dioxide has excellent light-scattering properties and adds white opacity and brightness. It's optical efficiency means that it provides these properties in an extremely efficient way with minimal impact on product quality and therefore long term durability of the coating, which reduces the environmental impact of paint. Although alternative white pigments are available these will have negative effects on product quality (minerals at high concentrations will lead to poor performance in adhesion, durability, stain and dirt resistance, exterior durability to name a few) or health (e.g. Lead Carbonate). We have been using titanium dioxide for many years without incident. Engineering measures such as Local Exhaust Ventilation (LEV) are in place in our manufacturing facility and all of our operatives wear the appropriate PPE when handling all raw materials such as dust masks when handling powders. We support the pragmatic risk based views of the Titanium Dioxide Manufacturers Association (TDMA) that once titanium dioxide is bound within a liquid matrix such as paint there is no longer a risk of inhalation of powder and the classification as a Category 1B carcinogen should not apply. If paints containing titanium dioxide were restricted to professional use only then we would not be able to trade in our current format. We would have to provide Trade only products which would severely limit their use and impose extra cost burdens on people who wish to be decorate and protect their homes. If we were to reformulate our products to be free of titanium dioxide to continue serving the consumer market, then customer satisfaction would be seriously impacted as the				

products would not offer the same levels of durability or longevity meaning that redecoration would be required more frequently which has negative impacts both financially and environmentally.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	Belgium	CEPE	BehalfOfAnOrganisation	301
Comment received				
CEPE represents the paint and printing ink industry in Europe and is one of the largest users of titanium dioxide (pigment), along with the plastics and paper industries. The combined annual turnover of our sector is >20 billion euros and about 130 000 people are directly employed by these industries. There are over one million industrial and professional downstream users of coatings and inks, and a significant proportion (estimated 15-20% of total GDP) of European industry relies on coatings and inks. Titanium dioxide is a constituent of over 85% of our members' products and thus any change to its classification will have a wide scale impact on our industry and on society. We are aware that the public consultation on the proposed classification should only consider toxicological arguments on inherent properties, and we refer to the work done by the TiO2 manufacturers, which we support. However, we would like at this early stage to alert Authorities to the consequences that a classification for TiO2 as a Carcinogen category 1B would cause, one of which being the non-availability of decorative paint to consumers(the consequence of the restriction on the placing of such products on the market according to REACH Annex XVII entry 28). In paint TiO2 is embedded in a liquid matrix and is not available to cause inhalation toxicity (should the alleged toxicological effects be confirmed) when the CLP Regulation classifies based on inherent properties only. This highlights once again the difference between hazard and risk, and the disconnect between hazard-based legislation and a real-life, pragmatic approach to the safe use of a finished product such as paint TiO2 is a unique pigment that offers opacity, whiteness, UV resistance and compatibility among other advantages. It is used from a few percent to +/- 40% in coatings and printing ink and has been used successfully for nearly a century. There is no alternative available that matches the performance of TiO2 in our products. In our industry we are not aware of cases of cancer due to exposure to TiO2, and studies by reputable organizations have repeatedly shown that the substance is safe to use. We believe that the consequences of the proposed classification would clearly be disproportionate to the risks posed to human health. We remain available to provide further information.				
Dossier Submitter's Response				
See points 1 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	Poland	GEHOLIT POLSKA Sp. z o.o.	BehalfOfAnOrganisation	302
Comment received				
We represent the Geholit+Wiemer GmbH located in the EU Member State of Germany and respond on behalf of that company. Our company currently employs about 200 people. As a producer of industrial and protective coatings we are concerned about the proposal made by France to classify titanium dioxide as carcinogen. TiO2 is a key material to our products with a maximum content of about 20%. We expect negative consequences of the proposed classification affecting strongly our pro-duction and our markets. With regard to the toxicological assessment we believe that the proposal is disproportionate and would have serious negative impacts on our company as well as on the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	Germany	Geholit+Wiemer Lack- und Kunststoff-Chemie GmbH	BehalfOfAnOrganisation	303
Comment received				
We represent the Geholit+Wiemer GmbH located in the EU Member State of Germany and respond on behalf of that company. Our company currently employs about 200 people. As a producer of industrial and protective coatings we are concerned about the proposal made by France to classify titanium dioxide as carcinogen. TiO2 is a key material to our products with a maximum content of about 20%. We expect negative consequences of the proposed classification affecting strongly our pro-duction and our markets. With regard to the toxicological assessment we believe that the proposal is disproportionate and would have serious negative impacts on our company as well as on the economy.				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Colorcon Ltd	BehalfOfAnOrganisation	304
Comment received				
It is Colorcon's position that the proposed classification and labelling of TiO2 as potentially carcinogenic by the inhalation route would not lower risks associated with the use of this substance but only create confusion and misplaced fear among consumers purchasing articles comprising TiO2 (especially food, dietary supplements and pharmaceuticals). The attached document explains in further detail our arguments: 1)potential inhalation				

hazards of TiO2 are already widely communicated to potentially affected parties; 2) there is no inhalation hazard for an individual consumer taking pharmaceuticals or eating foods comprising TiO2; 3)TiO2 has a long history of safe use in both the food, dietary supplement and pharmaceutical industries; and 4)adverse economic impact may result from unnecessary classification and labelling of TiO2. Colorcon recommends that there be no classification of TiO2 as a potential carcinogen via inhalation and any reports that are generated concerning this issue make it very clear that there are no safety concerns with using TiO2 in food and pharmaceutical applications where there is no potential for inhalation.

ECHA note – A non confidential attachment was submitted with the comment above. Comments from Colorcon to ECHA 24-June-16.pdf

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Speciality Coatings (Darwen) Ltd	BehalfOfAnOrganisation	305

Comment received

Our company has used Titanium Dioxide since 1986 at over 500 Tonnes per year without any health issues. We have had medical surveillance over most of that period and no problems have been recorded. Out of our workforce of 31, approximately 8 are exposed to the powder and use LEV and PPE. There is no dust or inhalation hazard once incorporated into a liquid PVC plastisol or subsequent wallcovering base we manufacture. Our business depends upon this material to provide opacity and whiteness to the products. It adds value. An alternative is 2x the price and half as effective so it would cost 4x overall and reduce our competitiveness globally. We fear any unjustified move to restrict or reclassify titanium dioxide would threaten the long term viability of the business.

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2016	United Kingdom	Steyport Ltd	BehalfOfAnOrganisation	306

Comment received

'I represent the company Steyport which was established in the EU Member State of the United Kingdom and respond on behalf of that company. We are a producer of Inks, Paints and Coatings and are concerned about the proposal made by France for classifying titanium dioxide as a carcinogen. Our company currently employs 40 people and we have been using this substance for 40 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers wear appropriate dust masks to protect themselves from dusty materials. When TiO2 has been incorporated in the bulk tank it is no longer available to be inhaled. TiO2 is a key material to manufacture our products. We understand that the consequence of the proposed classification would also

affect chemical mixture and we strongly believe that this would be disproportionate as it would have high economic impact to our company.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2016	Slovenia		Individual	307
Comment received				
I wonder, how can ECHA as European agency accept proposal of a single national institution, which completely ignores numerous EC funded projects in the field of nano safety and their conclusions (e.g. NanoValid, MARINE ...). What is the point of spendindg hundreds of millions of euros for these projects if then even European agencies don't even consult them or involve them into consultation on specific regulatory proposals with potentialy enormous impact on nanotecnology, whole range of industries and wide range of other European stakeholders? In that sense it is irresponsible of the agency to launch a public discussion of the proposal with out considering current state of the art and without European wide expert pre-evaluation (Nano Safety cluster could offer appropriate guidance and support to ECHA).			
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2016	Ireland		Individual	308
Comment received				
Thank you very much for sharing the below information with us and for the opportunity to provide our comments regarding the proposed harmonized classification of titanium dioxide (TiO2). We, as a manufacturer of formulated ceramic dielectric compositions for the electronic industry worldwide, have found the proposal to register TiO2 as an inhalation Cat 1B carcinogen very concerning because it may cause a significant negative impact on our business. Yes, we are aware that TiO2 dust has been already classified by the International Agency for Research on Cancer as an IARC Group 2B carcinogen, meaning it is possibly carcinogenic to humans. According to an industrial statistic, over 80% of the world's TiO2 consumption goes into the production of paints, plastics, rubber, cosmetics, and foodstuffs, where TiO2 is used and remained in the products as a single phase compound in a powder form. On the other hand, titanium dioxide, used in formulated ceramic dielectrics, is pre-reacted with other chemical compounds at high temperatures and, as a result, is much less active compared to the single phase TiO2 in the powder form. The pre-reacted TiO2 is not the same as the TiO2 dust! If ECHA decided to classify TiO2 as Cat 1B carcinogen, a substance presumed to have carcinogenic potential for humans, it would potentially cause a significant concern among customers and hurt not only businesses which products contain the single phase TiO2 in the powder form, but also the businesses which products contain the pre-reacted TiO2 used as the part of more complex chemical compounds. We believe that the pre-reacted TiO2 used in the formulated ceramic dielectric compositions should be exempted from classification as Cat 1B carcinogen.				

Dossier Submitter's Response
See points 1 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.06.2016	France		Individual	309
Comment received				
d'abord je parle français, et ne comprends pas ce qui est dit sur ce formulaire théoriquement destiné à plusieurs nationalités, qui devrait être traduit. Sur le fond : je relève cela et je ne vois même pas comment on ose demander aux gens s'ils sont prêts à le subir : Les données actuellement disponibles, telles qu'analysées par l'Anses, démontrent que le dioxyde de titane peut entraîner des tumeurs malignes chez le rat après une exposition par inhalation. Un niveau de preuve suffisant permet de considérer le dioxyde de titane comme cancérogène avéré chez l'animal au vu des données expérimentales. Chez l'Homme, le caractère cancérogène reste débattu du fait de limites méthodologiques des études épidémiologiques disponibles. En raison de ses propriétés physico-chimiques, une exposition par voie respiratoire au dioxyde de titane, à un certain niveau de concentration, peut entraîner une surcharge pulmonaire et conduire à une réaction inflammatoire, à l'origine de lésions prolifératives.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Italy	URAI S.p.A.	BehalfOfAnOrganisation	310
Comment received				
We are distributors of titanium dioxide in the italian market. We began distribution 50 years ago. In all this time we have never had information of health problems from our customers. The distribution of titanium dioxide is very important for our company. The proposed classification will cause wery serious problems, because there are not any suitable alternative products available.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Germany	Stockmeier Urethanes GmbH & Co. KG	BehalfOfAnOrganisation	311
Comment received				
TiO2 has been used by our company for many years without any problems. If the classification is agreed upon we are facing serious problems, because there are no suitable substitute raw materials available. Ultimately, our product range would be				

significantly reduced. This will lead to significant loss of business and might ultimately also lead to loss of jobs. Also, acceptance of this classification might lead to similar actions regarding the use of other powders and dusts, e. g. Aerosil type fillers, ATH, Calcit, Dolomit etc. The effect on many industries would be severe.
Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	312
Comment received				
BECA thanks ANSES for this C&L proposal. At present there is one registration for "titanium dioxide" which covers "all crystal phases&hydrates of titanium dioxide including rutile, anatase, monohydrate and dihydrate". If such registration is accepted and if all possible variations are considered equivalent in terms of hazard profile, BE CA is of the opinion that all TiO2 structures should be classified as Carc. 1B, H350i. However, BE CA is of the opinion that the size, shape, crystal structure, surface area, … has an impact on the level of oxidative stress and may play a role in the carcinogenicity. Studies suggest that anatase might be more carcinogenic than rutile TiO2. Moreover, the guidance on application of CLP criteria indicates that "A substance category is a group of substances whose physico-chemical, human health, environmental and/or environmental fate properties are expected to be similar or to follow a regular pattern as a result of structural similarity. Classification of all substances within an initially considered category may be inappropriate as substances may fall into more than one hazard classification category." Therefore BE CA does not agree with the grouping of all TiO2 and suggests that the different types are considered separately. BECA would like to emphasize that some publications are not integrated in the CLH proposal : • Trouiller et al., 2009 : mice were given 21 nm diameter TiO2 nanoparticles (75% anatase, 25% rutile) at 500 mg/kg bw in drinking water which led to clear genotoxic effects as evaluated by both the in vivo Comet assay and micronucleus assay. The clear genotoxic effects at the dose lower than those described above indicates that there is a potential carcinogenic effect for TiO2 nanoparticles through oral exposure. • Park et al., 2009 : used 25 nm diameter mixed (80% anatase, 20% rutile) nanoparticles and found an increase in granuloma frequency in ICR mice. This study confirms that small-sized anatase TiO2 indeed appears to possess a carcinogenic effect. References : Trouiller B, Reliene R, Westbrook A, et al. "Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice". Cancer Res;69:8784e9, 2009. E. J. Park, J. Yoon, K. Choi, J. Yi, and K. Park, "Induction of chronic inflammation in mice				

treated with titanium dioxide nanoparticles by intratracheal instillation," Toxicology, vol. 260, no. 1–3, pp. 37–46, 2009.
Dossier Submitter's Response
See point 1 of the attachment to the RCOM. Specific response: Trouiller *et al.* (2009) is already present in the reference list of the CLH report. Park *et al.* (2009) is related to inflammatory response and does not specifically assess carcinogenicity. However, this publication is in line with other publications showing that TiO_2 induce inflammation.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Portugal	Portuguese Paint Association	BehalfOfAnOrganisation	313
Comment received				
We support the work behind the toxicological comments made by the Titanium Dioxide Manufacturers Association (TDMA).				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany	Protec Systempasten GmbH	BehalfOfAnOrganisation	314
Comment received				
We have been using this substance for 21 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Netherlands		MemberState	315
Comment received				
It is agreed that human data are insufficient to classify titanium dioxide as Carc. 1A. Carcinogenic effects are only observed after inhalation of high doses of TiO2 in rats, but				

not in mice. This difference in carcinogenic response between rats and mice (and hamsters) is in line with the results observed for other non-soluble particles. However, comparison of these three animal models on their predictivity of known human lung carcinogens in general indicates that the rat is the best model. Non-carcinogenic effects of lung overload (e.g. inflammation) were also observed in mice. In addition, only local tumours have been observed. This is consistent with the proposed mechanism of secondary genotoxicity caused by inflammation and induction of oxidative lesions due to lung overload.
Since both benign and malignant lung tumours were reported in different studies (although in 1 species), Carc. 1B is proposed by the dossier submitter.
It might be argued that, since there is still no consensus in the international scientific community with regard to the relevance of carcinogenic effects in rats at overload conditions for humans, this is reason for classification in Carc. 2 instead of Carc. 1B. However, the criteria also allow classification in category 1B in case of several positive studies in the same species. This is strengthened by the fact that a direct genotoxic mechanism cannot be totally excluded, especially considering the positive results observed in several genotoxic studies (including in vivo tests, especially for nano forms). Overall, this is considered a borderline case between category 1B and 2 but we agree with the France proposal.
The specification of the route of exposure (i.e. inhalation) is agreed with.

With regard to types and forms, although the limited data available indicate that some sizes or forms may be more reactive than others, there is no reason to assume that the carcinogenic properties observed are limited to some specific forms of TiO2. The proposed classification is therefore considered relevant for all the forms included in the scope of the dossier.

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Japan	Japan Chemical Industry Association	BehalfOfAnOrganisation	316

Comment received

・According to two inhalation studies in rats, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumors, and adenocarcinoma were observed only in female rats, whilst no increase of carcinogenesis or the increase of mortality was recognized in other two studies in rats or a study in mice. In addition, in the two inhalation studies in rats mentioned above, the rats were exposed to titanium dioxide at concentrations of 0, 10, 50 and 250 mg/m3, showing that the maximum dosage caused bronchioalveolar adenoma, and it was suggested that this was the influence of overloading (Lee, 1985 R2). As it is known that pulmonary responses to inhaled particles of TiO2 differ by species, we consider that it is inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans.
・The above-mentioned animal studies were referred to in IARC Monograph 93(2010) and they are not particularly new evidence. It is thought that these are insufficient to assume that TiO2 should be given the carcinogenic classification 1B for (2A equivalency of the IARC classification).
・There are many epidemiology studies on carcinogenicity in humans in Europe and North

America. However, sufficient evidence was not shown regarding the carcinogenicity of TiO2 in humans.

ECHA note – A non confidential attachment was submitted with the comment above. TiO2_CLH_20160715_JCIA_EN Final.pdf

Dossier Submitter's Response

See points 2 and 5 of the attachment to the RCOM.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	317

Comment received

As a European citizen that owns an old-fashioned house with walls that are mainly surface-treated with Titanium dioxide I am really concerned about the proposal to classify this substance as Carcinogenic 1B and at least want to have expressed my personal opinion.

To my best knowledge inhalative exposure to Titanium dioxide is limited to work place situations. The relevant OEL in Germany (General dust limit) already covers effects that might be caused in humans due to lung overload conditions and thus exemplary controls any risk for human health from poorly soluble particles. I acknowledge the European position to clearly distinct between risk and hazard, however, reading the CLH proposal by France I cannot conclude for an evident human health hazard. Using any small but remaining uncertainty ("You can never prove the negative") to identify an abstract hazard, in my view, is not the right way for substances that have such a high socio-economic impact and where risk for human health is (or can be) sufficiently controlled by other means. Moreover, I am of the opinion that uncertainty can drastically be reduced to an regulatory acceptable level by also accepting scientific evidence that rat lung tumors under overload conditions are with high certainty not relevant for human health, irrespective of the particle size. Therefore, I propose to thoroughly consult the following literature:

ECETOC (2013): Poorly Soluble Particles / Lung Overload, Technical Report 122

Gebel T. 2012. Small difference in carcinogenic potency between GBP nanomaterials and GBP micromaterials. Arch. toxicol. 86:995-1007

ILSI Risk Science Institute. 2000. The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. ILSI Risk Science Institute. Inhal. Toxicol. 12:1-17

Nikula KJ, Avila KJ, Griffith WC, Mauderly JL. 1997. Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. Fundam. Appl. Toxicol. 37:37-53

Valberg PA, Bruch J, McCunney RJ. 2009. Are rat results from intratracheal instillation of 19 granular dusts a reliable basis for predicting cancer risk? Regul. Toxicol. Pharmacol. 54:72-83

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Carbon Black For REACH Consortium	BehalfOfAnOrganisation	318

Comment received

Outline

I. Introduction
A. Background/interest in topic; scientific advisory group's perspective of a substance also considered a PSP: carbon black
II. Commentary regarding ANSES's assessment of lung overload
A. ANSES: Implications of lung overload in laboratory rats for human health risk assessment.
B. Carbon Black for REACH Consortium's Response to ANSES commentary on use of rat overload results data for human risk assessment
B1. Mechanism of the Rat Lung Response to Particle Overload
B2. Pulmonary Response in Mammalian Species Other Than Rodents
B3. Species-specific response to poorly soluble particles
B4. Differences in Broncho alveolar lavage (BAL) findings in rats and humans
B5. Summary of implications of lung overload in rats for human risk assessment
III. Review of Epidemiology Studies: Contrasting the experience of laboratory rats with humans
A. ANSES CLH Report does not discuss Coal Miner Epidemiology Studies or any PSP Epidemiology Study
B. Workers with potential lung overload: Coal Miners
C. Workers exposed long-term to poorly soluble particles: Carbon Black Manufacturing
D. Workers exposed to Toner and Titanium dioxide: No lung cancer excess risk in workers
E. Summary: Weight of evidence assessment of epidemiology literature
IV. Conclusions
V. References
VI. Appendix
A. Comments on the GBS document of the German MAK Commission
B. Comments on the "Respiratory disease mortality among US coal miners; results after 37 years of follow-up" by Graber et al., 2014

I. Introduction
A. Background/interest in topic; scientific advisory group's perspective of a substance also considered a PSP: carbon black
The Carbon Black for REACH Consortium (CB4REACH) offers comments on the CLH report, submitted by ANSES and proposing a harmonised classification and labelling for Titanium dioxide (TiO2) for the carcinogenicity endpoint (ECHA 2016). Scientific and medical experts of the Scientific Advisory Group (SAG) of the International Carbon Black Association (ICBA) developed these comments on behalf of the CB4REACH Consortium. As members of ICBA's SAG, we have overseen and conducted numerous peer-reviewed epidemiology, toxicology and industrial hygiene studies related to carbon black (CB), a substance often described - like TiO2- as a poorly soluble particle (PSP).

We offer these comments as many of the scientific issues raised in the ANSES CLH report are based, not only on TiO2, but on other respirable PSPs, including CB, a substance which has been extensively investigated, through CB-exposed production worker studies for mortality and morbidity endpoints as well as through many informative rodent inhalation studies and in vitro investigations.

We specifically comment on three key aspects, namely:

(1) ANSES's evaluation of the significance to humans of lung overload endpoints in laboratory rodents; and in particular lung cancer in the rat; and

(2) An evaluation of the epidemiology literature of coal miners as it relates to lung overload in rats. In general, ANSES concludes that rat inhalation studies in which lung overload is associated with cancer should be used in human risk assessment, most notably for risk of lung cancer. The ANSES report, however, ignores the vast literature of mortality studies of TiO2, coal miners and CB production workers, in which lung cancer risk was not elevated, even among the most heavily exposed coal miners who developed Coal Workers pneumoconiosis (CWP) or in the TiO2 and CB production workers.

(3) The overall evidence base does not meet the CLP criteria for classification for carcinogenicity of Carc. Cat 1B – H350i as proposed in the ANSES draft document.
II. Commentary regarding ANSES's assessment of lung overload
A. ANSES: Implications of lung overload in laboratory rats for human health risk assessment.
In the ANSES TiO2 document, it is stated: "This CLH report therefore focuses on carcinogenicity of TiO2. Indeed, because the carcinogenic mode of action of TiO2 seems to be rather due to inflammatory process and oxidative stress, it is believed that biopersistence and solubility are relevant to explain this toxicological effect….Indeed TiO2 in all these combination is considered to behave in the same way as other poorly soluble low toxicity particles (e.g. coal dust, diesel exhaust particulates, toner …). This statement does not preclude that some parameters (in particular shape and coating) might also lead to a more potent carcinogenicity or to other specific lesions via a specific mode of action. The proposal presented below is based on data considered sufficient by MSCA-FR to propose a general entry for classification of TiO2 for Carcinogenicity by inhalation. In case new data is available, the entry may be modified upon submission of these data by the registrant."

Comment:
The above reasoning by ANSES is that rat lung tumours, seen with TiO2 and other PSPs (such as CB), is predictive of human risk. However, the evidence from other rodent species (such as mice and hamsters) and a wealth of relevant and well-conducted epidemiological investigations, not addressed in the ANSES report, strongly supports the contention that the lung tumour response, seen in rats, is unique to that species under overload conditions and related to an exaggerated inflammatory response causing a secondary (non-direct genotoxic) carcinogenic mode of action (Morfeld et al., 2015; ECETOC 2013).

In their report, ANSES justifies its carcinogenicity classification of TiO2 based on studies of laboratory rats. In the section on "Carcinogenicity", the report states: "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable,"

Comment:
However, the ANSES report provides no detail or epidemiological evidence from the many available studies to support this broad and dismissive conclusion. We find it totally inappropriate to dismiss such a large body of well-conducted peer-reviewed investigations into occupational exposure to TiO2 and other relevant occupational studies with PSPs.

The ANSES report then describes the results of the animal studies in more detail.

"In experimental animal studies, lung tumours were reported after inhalation or intra-tracheal administration of in rats in an overload context. Overload is defined by an impairment of normal pulmonary clearance due to high accumulation of particles. Although inter-species variability was found in particle retention, the overload concept is relevant for humans, and in particular for workers exposed to high dust concentrations.

Comment:
To support this contention, it would be appropriate for ANSES to define what they mean by "high dust concentrations" and to define criteria for overload.

Furthermore, it appears that lung retention and chronic pulmonary inflammation occurring in humans are consistent with the findings in rats."

Comment:
We note that this latter statement in the ANSES report is inconsistent with the scientific literature (described later.)

"Although benign lung tumours (bronchioalveolar adenomas) were observed in both sexes, malignant tumours (squamous cell carcinomas and bronchioalveolar adenocarcinomas) were only reported in female rats… Based on these effects, IARC (2006) concluded that there is sufficient evidence that TiO2 is carcinogenic in animals.

Although the full mode of action is still unclear, an inflammatory process and indirect genotoxic effect through ROS production seems to be the major mechanism to explain the effects induced by TiO2. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO2 particles. However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO2 was found in the cell nucleus in various in vitro and in vivo studies".

Comment:
We feel that it is unhelpful for ANSES to state that at "a genotoxic effect by direct interaction with DNA cannot be excluded…" as clearly, one cannot ever prove a negative and the overwhelming in vitro and in vivo studies demonstrate that TiO2 is not directly genotoxic.

The proposed mechanism is already described for other substances such as aluminium oxide, insoluble nickel salts and iron oxides, acting as poorly soluble low toxicity particles, which elicit lung tumours in rats following prolonged exposure at sufficiently high concentrations.

Therefore, classification as Carc. Cat 1B – H350i is justified for TiO2 considering the increase of both malignant and benign lung tumours in one species, reported in two studies by inhalation and two studies by instillation after exposure to TiO2."

Comment:
Our considered view is that if one used a weight of evidence approach, as recommended

by ECHA in its Guidance on information requirements and chemical safety assessment - Chapter R.4: Evaluation of available information, and envisioned by the CLP regulation (section 1.1.1 of Regulation (EC) No 1272/2008), and included epidemiological studies, experimental interspecies differences and mode of action findings and accepted that lung tumours induced by PSPs such as TiO2, were unique to the rat and not predictive for humans, then no classification would seem far more appropriate and consistent with the science base.

ANSES mentioned the GBS approach of the German MAK Commission in favour of a cancer classification of TiO2. We draw attention to the review by Morfeld et al., 2015 that discusses the scientific shortcomings and lack of reproducibility of the MAK approach and to the fact that these limitations of the GBS approach were not discussed by ANSES. We refer readers to Appendix A for details.
B. Carbon Black for REACH Consortium's Response to ANSES commentary on use of rat overload results data for human risk assessment
B1. Mechanism of the Rat Lung Response to Particle Overload
CB is a PSP similar to TiO2; therefore it is useful to evaluate pulmonary studies on CB as the results are directly relevant to TiO2. In numerous studies, rodents, particularly rats, have been exposed by inhalation to CB. Based on the results from these studies a number of conclusions may be drawn.

First, prolonged inhalation of high levels of CB causes delayed pulmonary clearance and marked retention of particles. This phenomenon is described as "lung overload" (IARC 1996; Mauderly, 1996) and is common for a range of respirable insoluble dusts of low toxicity (PSPs). The sequelae to these high lung burdens in rats include inflammation, which leads to a range of changes in pro- and anti-inflammatory biochemical parameters (found in bronchoalveolar lavage fluid), epithelial hyperplasia, and pulmonary fibrosis.

Second, rats are more sensitive to the effects of CB overload than other species; with female rats having more pronounced reactions than male rats (ILSI, 2000). In long-term studies, only female rats were prone to a significant increase in the development of lung tumours. The lowest CB concentration used in a chronic inhalation study where lung tumours were induced was 2.5 mg/m3, with rats being exposed for 16 hours/day, 5 days/week for 2 years (Nikula et al., 1995). However, mice exposed to 11.6 mg/m3 CB for 18 hours/day, 5 days/week for 13.5 months and observed for a further 9.5 months did not exhibit an increase in lung tumours (Heinrich et al., 1995). In primates (Nikula et al., 1997) and in humans (Mauderly 1996), there are clear differences in particle deposition, clearance patterns, and tissue reactions, when compared to rats. These differences underline the uniqueness of the rat tumour development under conditions of lung overload and raise questions as to the validity of interspecies extrapolations of particle effects from rats to humans.

Third, results from genotoxicity studies suggest a direct association of mutation with inflammation and its sequelae in rat lung tumour development. Lung inflammation leads to the production of reactive oxygen species, and these mutational lesions seen in the ex vivo hprt assay can be prevented by experimental treatment with antioxidants (Driscoll et al., 1997). This study demonstrated that the increase in mutation frequency is caused by oxidative damage alone, typical of a secondary genotoxic mechanism.

The prevailing scientific consensus is that rat lung tumours induced by inert, PSPs, such as CB and TiO2, arise out of a background of chronic and persistent inflammatory changes; the corollary being that if these changes are avoided, then the tumours will not occur (ECETOC 2013). In this respect, the studies of Driscoll et al., (1996) are of particular relevance because exposure to 1.1 mg/m3 of respirable CB particles did not

evoke inflammatory or mutational changes to female rats. A no observed adverse effect level (NOAEL) of 1 mg/m3 (respirable) CB is supported by other rodent findings by Oberdoerster, Driscoll, and colleagues (Carter et al., 2006, Elder et al., 2005; Driscoll et al., 2002; ILSI, 2000).

To summarize, the major rodent interspecies differences in lung responses to inhaled CB particles are:

a) the pulmonary clearance of CB particles was significantly faster in hamsters vs. rats or mice;
b) exposures to higher concentrations of CB produced particle overload in the lungs of both rats and mice;
c) the pulmonary cellular and tissue responses to particle overload were different in the rats when compared to similarly exposed mice – i.e., rats developed greater and sustained lung inflammatory responses and significantly more intensive epithelial and fibro-proliferative responses.
B2. Pulmonary Response in Mammalian Species Other Than Rodents
In studies reported by Nikula et al., (1997, 2001), it is proposed that the intrapulmonary particle retention patterns and tissue reactions in rats may not be predictive of pulmonary retention patterns and tissue responses in either primates or humans. Male cynomolgus monkeys and F344 rats were exposed for 7 hours/day, 5 days/week for 24 months to diesel exhaust (2 mg/m3), coal dust (2 mg/m3), or diesel exhaust and coal dust combined (1 mg/m3 each) and were subsequently examined histopathologically (Nikula et al., 1997). In all exposed groups, monkeys retained a similar amount or more particulate material in the lungs than did rats. Rats retained a greater proportion of the particulate material in the alveolar ducts and alveoli, whereas monkeys retained a greater proportion of particulate material in the interstitium. Rats, but not monkeys, had significant alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses to the retained particles.

In a subsequent study, Nikula et al., (2001) evaluated the influence of exposure concentration on the distribution of particulate material within the lungs of rats and humans. In this study the investigators used morphometric methods to assess the influence of exposure concentration on particle retention by evaluating histological lung sections from rats and humans. The rats had been exposed for 24 months to diesel exhaust at 0.35, 3.5, or 7.0 mg/m3. The human subject groups included: 1) non-smokers who did not work as miners; 2) non-smoking coal miners who worked under the current standard of 2 mg dust/m3 for 10-20 years; and 3) non-smoking coal miners who worked under the former standard of <10 mg dust/m3 for 33 to 50 years. The distribution of retained particles within the lung compartments was markedly different between species. In all three groups of rats, 82 to 85% of the retained particulate material was located in the alveolar and alveolar duct lumens, primarily in macrophages. In humans, 57, 68, and 91% of the retained particulate material, respectively, was located in the interstitium of the lung in the three aforementioned study groups. The authors concluded: "These results show that chronically inhaled diesel soot is retained predominantly in the airspaces of rats over a wide range of exposures, whereas in humans, chronically inhaled particulate material is retained primarily in the interstitium. In humans, the percentage of particles in the interstitium is increased with increasing dose (exposure concentration, years of exposure, and/or lung burden). This difference in distribution may bring different lung cells into contact with the retained particles or particle-containing macrophages in rats and humans and, therefore, may account for differences in species response to inhaled particles."

A comprehensive review on translational toxicology focusing on PSP exposure and on CB,

as one example, was published by Morfeld et al., in 2015.
B3. Species-specific response to poorly soluble particles
It is possible to explore the species differences using the Mode of Action, the AOP (Adverse Outcome Pathway) and events at the molecular level to better refine the way translational toxicology is used to exchange experimental findings between rodent species, primates and human responses to PSPs. From the wealth of available data, it seems too simplistic to simply assume that what occurs in the rats can be assumed to occur in humans without carefully taking into account both critical toxicokinetic and toxicodynamic differences. This means that we have to take into account the totality of the available information at the anatomical, physiological, cellular and molecular level in a reliable translational exercise. Rats have been consistently shown to have a more sensitive response to the chronic inhalation of respirable particles compared to other species, and a unique response in relation to lung cancer. The species-specific differences in responses are summarized in Table 1. Thus, in agreement with ECETOC (ECETOC, 2013), mechanistic data are available to overcome the default statement made by the ILSI panel in 2000 (ILSI, 2000) and cited in Kuempel et al., 2014. This conclusion is consistent with findings from studies on humans.
Table 1: Interspecies lung responses a following long-term or chronic inhalation exposure to granular biopersistent substances (=PSPs)
Species
Rat Mouse Hamster Primate/Human
Likelihood for developing particle overload (slow lung clearance)
+++ +++ + Not determined*
Alveolar macrophage participation
Active (accumulation in alveolar ducts) Active (accumulation in alveolar ducts) Extensive (rapid clearance) Not as extensive (translocation to interstitial sites)
Pulmonary (neutrophilic) inflammation
+++ +++ + +
Epithelial and interstitial cell proliferation
+++ + (+) (+)
Septal fibrosis
+++ + (+) (+)
Anatomical location of retained particulates
Primarily alveolar (some increased translocation at overload) Primarily alveolar (some translocation at overload) Rapid clearance Primarily interstitial
Lung tumours following chronic exposure
Yes No No No
a Severity low +, moderate ++, high +++, or questionable (+), reprinted with permission from [ECETOC 2013, p. 52]**
*This should be + (see page 53 in ECETOC 2013 because particle overload is typified by an impairment in alveolar particle clearance (see pages 1 and 4 in ECETOC 2013.
**There may be a variance of opinion about the extent/degree of some of the endpoints in the table (e.g., alveolar macrophage participation, septal fibrosis) and there is continuing research to refine these findings.
Variable responses, at the cellular and molecular levels, as well as regarding tumour development (defence systems) are seen in mice, hamster, rats, and primates following particle exposure. It is thus important to ascertain how these models perform, in a translational exercise between these three and possibly other species, to verify the "species independent" assumption.
B4. Differences in Broncho alveolar lavage (BAL) findings in rats and humans
BAL studies in humans are consistent with epidemiological results of workers. BAL is a widely used clinical diagnostic study in the evaluation of lung disorders, particularly in the differentiation of interstitial lung diseases (ILD). In light of the emphasis given in the ANSES CLP report and also by others such as the MAK Commission (Hartwig et al.,

2012), to data from rat experiments, it would be valuable to determine whether corresponding biomarkers can be identified in human BAL fluid of dust-exposed people.

BALF on coal workers were assessed for their cellular profile (Kayacan et al., 2003; Xing et al., 2006; Vallyathan et al., 2000; Vanhee et al., 1994; and Vanhee et al., 1995). Epidemiological data do not provide convincing support for an increased lung cancer risk in people exposed to high dust levels, such as coal miners. Epidemiological findings contrast with the results of experimental studies on rats, in which at higher exposure levels, excess lung tumours were detected. Chronic inflammation is the underlying mechanism, which causes secondary genotoxic events by oxidative damage due to inflammatory cells.

Groups of miners with different stages of coal workers' pneumoconiosis (CWP) were compared (posterior-anterior chest radiographs, ILO resp. Chinese x-ray staging of CWP). No increased counts for PMNs were detected in asymptomatic miners and in miners with low grades of simple pneumoconiosis, i.e., CWP ≤ 1/1 (Kayacan et al., 2003; Xing et al., 2006)]. One group of miners with simple pneumoconiosis showed an elevation of the neutrophil percentages in the BALF in comparison to controls (Vanhee et al., 1994). In contrast, a second group studied by the same researchers showed almost the same average neutrophil percentage as reported for controls Vanhee et al., 1995)].

Xing et al., 2006, studied biomarkers in the BALFs of coal mine workers: 14 active underground miners without CWP, 21 workers with CWP 0/1, and 13 no longer exposed workers after cessation of exposure with CWP 1/1. None of the groups showed elevated neutrophils numbers (PMNs). However, other biomarkers in the BALF of the coal workers were clearly changed; for instance, markers of the epithelial reaction (pneumocyte type II): (a) increased surfactant lipids, (b) altered ratio of PG/PI (subgroups of lung surfactant: phosphatidyl glycerol PG, phosphatidyl initisol PI), (c) increased surfactant protein A. The elevated TNF alpha content in the BALF (d) stands for the effect of the phagocytosed particles on AM. Interestingly, the results on parameters (a, b, d) correspond to findings in dust-exposed rats, e.g., the increased surfactant lipids, the altered ratio of PG/PI, the elevation of TNF alpha (Adachi et al., 1989; Nehls et al., 1997; Seiler et al., 2001) It is worth mentioning that rats exposed to coal dust showed a significant increase of PMNs in the BALF (Donaldson et al., 1990).The investigations of Vanhee et al.,1995 identified different profiles of growth factors (PDGF, IGF1, TGF beta) in the BALF of coal miners according to the severity of x-ray changes. Further, in vitro and in vivo studies on human (BALF) alveolar macrophages from patients with different grades of pneumoconiosis clearly demonstrated the eminent role of the AM for the onset and development of the coal miners' lung disease. Mixed CS and coal dust exposures eventually trigger an aggressive form of pneumoconiosis and BALF pattern (Vallyathan et al., 2000) The miners´ individual working-lifetime exposures (n = 20) were estimated from this study, using work histories and airborne mine dust data. The quartz lung-burdens were calculated using a lung dosimetry model. The study showed that quartz, either as cumulative exposure or as calculated lung burden, was a highly significant predictor of PMN lung response. The cumulative coal dust exposure did not contribute to the prediction of PMNs (Kuempel et al., 2003)

An American Thoracic Society (ATS) clinical practice guideline on the utility of BALF cellular analysis summarized for CWP that BALF cell profiles, indicative of increased numbers of macrophages and elevated proportion of coal dust-laden macrophages, are suggestive of CWP or progressive massive fibrosis (PMF) (Meyer et al., 2012) The authors stated for silicosis that BALF profiles of silica-exposed workers and workers with silicosis are characterized by an excess in BALF macrophages and an increased silica particle burden of macrophages that is appreciable in non-smokers. Meyer et al., 2012, made no

recommendations regarding the clinical utility for prognosis of CWP or PMF. The authors noted the prognostic value for silicosis that increased numbers of lymphocytes and neutrophils have been associated with progression to silicosis.

In conclusion, the prominent role given to the BALF-PMNs in relation to the particle lung exposure in rats does not correspond to BAL results in humans. Human data reflect a significant role for the alveolar macrophages and type II pneumocytes in the development of dust induced interstitial lung diseases (ILDs) in humans, a role also played in rat studies (Rom et al., 1987). The PMNs, however, play a unique role in rat experiments, findings that do not appear to occur in high dust (PSP) exposed workers, such as coal miners. In conclusion, the human BAL biomarker studies corroborate the epidemiological findings.

B5. Summary of implications of lung overload in rats for human risk assessment

Although lung tumours are induced in rats when exposed to CB, it is generally acknowledged that these tumours are produced because of the lung overload phenomenon, a point noted in the ANSES CLP report as well. When exposed to a PSP such as CB in high concentrations, laboratory rats cannot adequately clear CB from their respiratory tract, so lung tumours are induced by a secondary non-genotoxic mechanism. Lung tumours were not observed in mice and hamsters under similar study conditions. The relevance of the rat tumour data to human risk assessment has been raised in an earlier review of the animal literature at a consensus conference of investigators (ILSI, 2000). An updated review by ECETOC (2013) also concluded that the rat represents a unique model with regard to lung neoplastic responses under conditions of lung overload: "The rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload." (ECETOC 2013).

In support of this above opinion, it should be noted that in ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2015), the issue of lung overload is mentioned under section 3.9.2.5.3, Mechanisms not relevant to humans (CLP Annex 1, 3.9.2.8.1 (e)) as "The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate". Also section 3.9.2.8.1 (e) of Annex 1 of CLP states that "Substance – induced species specific mechanisms of toxicity substance, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification". Further, section 3.6.1.1 of the CLP regulation states "Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans."

Section 1.1.1.4 of Annex 1 of the CLP regulation states that "Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data." It is our considered view that the overwhelming evidence from well-conducted occupational epidemiological investigations on workers exposed to a range on PSPs, including carbon black, TiO2 and coal mine dust, are adequate, reliable and representative human data, and provide, "strong evidence that the mechanism of tumour formation in the female rat is not relevant for humans". Therefore, in a weight of evidence assessment taking into consideration, epidemiological

findings, experimental interspecies differences, mode of action findings and accepting that lung tumours induced by PSPs such as TiO2, are unique to the rat and not predictive for humans, the classification for carcinogenesis Cat 1B – H350i proposed in the ANSES report is not defensible.

The ANSES CLP report states: "It should be noted that, although it cannot be directly transposable, there is a strong link between CLP and the IARC classification criteria since the definition of sufficient and limited evidence are part of the CLP criteria (guidance on the Application of the CLP criteria (version 4.1 – June 2015))." It should be noted that, the evaluation by IARC of carbon black and TiO2 as possibly carcinogenic to humans – Group 2B, is based solely on the observation that rats develop lung tumours under condition of "lung overload" and was in contradiction to the numerous negative epidemiological studies conducted on workers exposed to these two substances (both evaluated as inadequate by the IARC Working Group). The reliability of lung tumours induced in rats by inert poorly soluble particles, such as carbon black, as a predictor of hazard to humans is uncertain. Overall, the epidemiological evidence from well-conducted investigations has not shown that exposure to carbon black or TiO2 has a carcinogenic potential for humans (See detailed commentary later in this report CB mortality studies. The arguments regarding the uniqueness of rats in developing lung cancers under conditions of lung overload with PSPs (including TiO2 and CB) in contrast to other experimental species including non-human primates and in humans is succinctly captured in an Adverse Outcome Pathway table (Table 1), taken from ECETOC 2013, which is based upon the best available interpretation of the existing data

III. Review of Epidemiology Studies: Contrasting the experience of laboratory rats with humans

A. ANSES CLH Report does not discuss Coal Miner Epidemiology Studies or any PSP Epidemiology Study

In the ANSES document on TiO2, the authors do not contrast the human epidemiological literature on "lung overload" with the rat study results to gain a perspective on human risk assessment. ANSES bases its proposed carcinogenicity classification of TiO2 on studies of laboratory rats only. In the section on "Carcinogenicity", the CLH report states: "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable…." ANSES should provide an objective discussion of the many peer-reviewed epidemiological studies on PSPs in the scientific literature.

We draw the Committee's attention to ECHA's recent "Draft Guidance on information requirements and Chemical Safety Assessment Appendix R7-1 Recommendations for nanomaterials", where ECHA notes that a recent "epidemiological study evaluating the underlying cause of death for 9033 underground coal miners from 31 US mines after 37 years of follow-up (Graber et al., 2014), found a significant relationship between coal mine dust exposure and lung cancer mortality. Hence, the data obtained from rats may still be useful to predict the effects in humans." While we welcome ECHA's approach to include data on Epidemiology to inform their conclusion, it is surprising that ECHA does not review and consider other coal miners epidemiology data as well as the Graber et al., 2014 study. The Graber et al., (2014) study, which is "positive", is the only study cited by ECHA, out of the vast number of predominantly negative coal miner studies that are available, to emphasize the possible relevance of effects seen in rats under "overload" conditions for human hazard and risk assessment. Appendix B of this document provides a discussion of the Graber et al., 2014 study, placing it in perspective of the entire coal miner epidemiological studies. We draw the Committee's attention to the fact that the authors of this US study even acknowledged, in a reply to a Letter to the Editor, that

there are qualitatively better epidemiological studies available than their US coal miner study.

In the following section, we provide a comprehensive discussion of coal miner epidemiology studies. The results of these studies indicate that PSPs, such as TiO2 do not increase cancer risk in humans.
B. Workers with potential lung overload: Coal Miners
Data on coal miners provide the best available human evidence with which to explore lung overload questions. Using eight studies conducted between 1956 and 1986 from a total of 1,225 miners in the US and UK, Mauderly (1994) converted the lung burden of coal dust into units of specific lung burden and showed that long-term coal miners commonly accumulated dust burdens in the range of 7 to 14 mg per g lung. This value indicates that the dust burdens in heavily exposed human lungs are in the same range as, or greater, than in the heavily exposed experimental animals seen in chronic bioassays. In spite of these high lung burdens, coal dust exposure has not been shown to significantly increase the risk of lung cancers among miners (IARC, 1996).

Coal miners do not suffer from elevated lung cancer risks (Stayner et al., 2011 and Morfeld, 2013). In an attempt to provide a perspective on risks of lung cancer under conditions of "lung overload", we reviewed mortality studies of coal worker and other dust-related industry cohorts. Exposure to coal mine dust particulate in miners has long been recognized as one distinct occupation with significant potential for exposure to dusts. It can be instructive to address the results of these studies in considering the potential human significance of high dose rat inhalation studies.

Intensive investigations in the US and in the UK showed that coal miners did not develop overload - even under high exposure conditions (Kuempel et al., 2001; Tran et al., 2014). Kuempel et al., 2001 studied pathologic data of 131 US coal miners (mean age at death: 67 years, average cumulative dust exposure: 107 mg-year/m3, 36 years of exposure, mean coal mine dust concentration: 3 mg/m3). The mean lung dust burden was 13.8 g (sd = 8 g) while the mean lymph dust burden, among the subset for which lymph data were available, was 1.6 g (sd = 1.6 g).

Tran and Buchanan analyzed the pathological data of 423 UK miners: mean age at death: 67 years, average cumulative dust exposure: 256 gh/m3 = 145 mg-year/m3 (assuming 220 working days per year with a shift length of 8 h) (Tran et al., 2014) The mean lung dust burden was 14.4 g (sd= 11.7 g) while the mean lymph dust burden, among the subset for which lymph data were available, was 2.3 g (sd= 1.0 g).

Kuempel et al., (2001) referred to a dosimetric model developed in 1997 and found that a three-compartment model with no clearance breakdown fit the lung burden best when analyzing the autopsy data of the US coal miners (Kuempel et al., 2001). Tran and Buchanan tested this hypothesis in their independent and larger set of 423 UK miners and produced the same result (Tran et al., 2014). A best fit was achieved when the alveolar clearance rate was set invariant, i.e., the two independent studies present convincing evidence that even under the historically-high dust exposure scenarios of coal miners, no lung overload occurred in humans (Kuempel et al., 2001 and Tran et al., 2014).This result and the related Gregoratto model (Gregoratto et al., 2010) were confirmed once more in a more recent study using both data sets in a Bayesian analysis via Markov Chain Monte Carlo simulations (Sweeney et al., 2013).

In the most recent study on US coal miners, the lung cancer standardized mortality ratio (SMR) was only slightly elevated (SMR=1.08, 95% CI: 1.00-1.18) (Graber et al., 2014). This excess is unexceptionable because of the higher proportion of smokers at the start of

the study in 1969/1970 (current smokers: 54%, Supplement Table IV) in comparison to the US male population in 1970 (current smokers: 44.1%). Internal analyses showed an association of lung cancer mortality with coal mine dust exposure but only during the last follow-up interval from 2000 to 2007. All follow-up periods until 2000 showed no association between coal mine dust exposure and lung cancer (Graber et al., 2014 and Attfield, 2008). The study relies on smoking information collected only at the start of follow-up. The models are unable to adjust for smoking habits after leaving work. Note that current smokers smoked less when working as a coal miner than current smokers in the US male population (prevalence of smoking more than 25 cigarettes per day: 12.4% among US coal miners vs. 28.0 % in the US male population). This difference is probably caused by prohibition of smoking when working underground. It is plausible that smoking coal miners have increased their intensity of smoking after cessation of work underground and that this may have caused an increase in lung cancer mortality during the last follow-up period when most coal miners of the cohort have already stopped working underground (See Miller et al., 2010). The US study has an incomplete assessment of jobs held; no start and end date of jobs/tasks held before 1969/1971; no information on jobs/tasks held after start of follow-up in 1979/1971 and no end date of working as a coal miner for 16% of cohort members (Graber et al., 2014). Thus, only a crude assessment of exposure to coal mine dust up to the start of follow-up was possible: no time-dependent exposure analysis or lagging or lugging of exposures could be done. Crystalline silica concentration data suffered from additional limitations because measurements were available only after 1982 but had to be allocated to the jobs held before 1969/1971. Shortcomings and errors of this study were discussed in two Letters to the Editor (Taeger et al., 2014 and Morfeld 2014). A detailed review of this study is noted in Appendix B)

The largest study to date with better assessment of exposures in a time-dependent manner was performed in the UK (Miller et al., 2010): the overall evidence does not support an excess in lung cancer risk among coal miners, when compared to the general population or in internal analyses of the effect of coal mine dust exposure (Graber et al., 2013). Similar results were found in Germany, based on a detailed and time-dependent exposure assessment in an analysis of lung cancer mortality and incidence data (Morfeld, 2013; Morfeld et al., 2002; Morfeld et al., 2004 and Morfeld et al., 2007).

We would like to emphasize that all coal miner mortality studies discussed in this section showed a link between coal mine dust exposure and coal worker's pneumoconiosis (CWP), a clear sign of substantial dust exposure and tissue reaction. Thus, even in the presence of pulmonary fibrosis, no increase in lung cancer was reported in relation to coal mine dust.

C. Workers exposed long-term to poorly soluble particles: Carbon Black Manufacturing

The mortality of CB production workers has been extensively studied in the USA and in Europe (Dell et al., 2015; Morfeld et al., 2006a ; Morfeld et al., 2006; Morfeld et al., 2007; Morfeld et al., 2009; Morfeld et al., 2010; Sorahan et al., 2001; Sorahan et al., 2007 and Wellman et al., 2006). Three major cohort epidemiological studies were performed in the UK, USA and Germany to investigate lung cancer mortality in CB production plants.

An update and extension of the retrospective mortality study of US carbon black workers evaluated a cohort of 6634 workers employed in the carbon black industry dating back to the 1930s (Dell et al., 2015). The mortality follow-up was extended until December 31, 2011 and a quantitative assessment of individual cumulative exposure to inhalable carbon black dust conducted. The results showed no increase in lung cancer or any other malignancy in either the total or inception cohorts: Lung cancer mortality was decreased in comparison to state-specific reference rates (184 observed deaths, SMR = 0.77; 0.95-CI: 0.67 to 0.89), and for all cancers (512 observed deaths, SMR=0.79, 0.95-CI: 0.72–

0.86). Internal exposure-response analyses showed no convincing link between carbon black exposure and lung cancer mortality. In summary, the authors of the study concluded: "Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or non malignant respiratory disease."

This retrospective US mortality study of carbon black workers is the largest cohort yet published in the world's literature. It includes over 6000 workers employed in the carbon black producing industry dating back to the 1930s. Both an inception cohort, designed to reduce potential survivor bias, and a total cohort were individually evaluated for mortality risks. A notable advantage of this epidemiology study is the detailed individual cumulative exposure assessments that were analyzed with uniform job titles to enable robust dose response analyses. The availability of nearly 30 years of actual carbon black airborne monitoring data back to 1979 facilitated calculation of reliable exposure estimates.
The results showed no increase in lung cancer or any other malignancy in either the total or the inception cohort. The dose-response analysis showed no link between carbon black exposure and risk of malignancy. Another notable advantage of this study is the exceptional level of ascertainment achieved in identifying vital status, in that 98.5% of eligible cohort members were identified as alive or deceased.
In summary, the authors of the 2015 study concluded: "Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or non malignant respiratory disease."
The most recent comprehensive international evaluation of potential human cancer risks due to carbon black (CB) exposures was performed by an IARC working group in February 2006 (Baan et al., 2006). The working group identified lung cancer as the most important endpoint to consider and exposures at CB production sites as the most relevant for an evaluation. Three major cohort epidemiological studies were performed in the UK, USA and Germany to investigate lung cancer mortality in CB production plants. These studies, all of which preceded the USA mortality study described above, were critically reviewed by an IARC working group in 2005. This same working group of scientists also reviewed the literature on TiO2 regarding its potential to cause cancer.
A UK cohort study on 1,147 workers at five plants (Sorahan et al., 2001) found a standardised mortality ratio (SMR) of 1.73 (61 cases, 0.95-confidence interval (CI): 1.32, 2.22) but no trend across crudely assessed cumulative exposure, lagged up to 20 years. Elevated lung cancer SMRs were observed at two plants, the SMRs of the other three plants were unexceptionable. A German study on 1,528 workers at one plant (Wellmann et al., 2006, Morfeld et al., 2006a, Buechte et al., 2006, Morfeld et al., 2006b) estimated an SMR = 1.83 (50 cases, 0.95-CI: 1.34, 2.39) but could not find any positive trends with CB exposures. However, the German study identified smoking and prior exposures to known carcinogens as important risk factors that could explain the major part of the excess risk (Morfeld et al., 2006a). A US cohort study on 5,011 workers at 18 plants (Dell et al., 2006) calculated an SMR = 0.85 (127 cases, 0.95-CI: 0.71, 1.00) and found no trend across time since first exposure and duration of exposure in years.

The working group at IARC concluded that the evidence in humans for the carcinogenicity of CB was inadequate (Baan et al., 2006; IARC 2006).

Since the IARC 2006 evaluation, in an extended follow-up of the UK study, Sorahan and Harrington (2007) applied a novel exposure metric ("lugging") while hypothesizing that CB may act as a late stage lung carcinogen at plants with elevated SMRs. If so, the elevated SMRs of lung cancer should decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative CB exposure ("lugging" the exposure by 15 years means to count only exposures received during the

last 15 years). Sorahan and Harrington (2007) observed both phenomena in those (and only those) two UK plant cohorts that had elevated lung cancer SMRs. The authors asked for repetitions of their surprising findings in independent settings. Morfeld and McCunney (2007) tested the hypothesis of Sorahan and Harrington (2007) in the German study. Neither a decreasing SMR after cessation of exposure was observed nor a positive relationship with "lugged" cumulative CB exposure although the German cohort showed a clearly elevated lung cancer SMR. Therefore, Morfeld and McCunney (2007) were unable to lend support to the new hypothesis generated by Sorahan and Harrington (Morfeld and McCunney, 2007).

More recent studies have also been published (Morfeld and McCunney, (2009 and 2010). In a detailed analysis of the German CB cohort, additional analysis was conducted to address potential "lugging" effects. As noted above, "lugging" is a term introduced by Sorahan and Harrington (2007) to account for the most recent exposures with respect to health risk. Methods such as Bayesian analysis were employed to explore all potential risk factors and confounders that may have contributed to the results. These additional studies provide further support for the lack of a significant increased risk of cancer as a result of working in the CB industry.

The relationship between workplace exposure to CB and lung cancer risk was examined in two large population-based case-control studies carried out in Montreal, Canada (Parent et al., 1996; Ramanakumar et al., 2008). Interviews for Study I were conducted in 1979–1986 (857 cases, 533 population controls, 1,349 cancer controls) and interviews for Study II were conducted in 1996–2001 (1,236 cases and 1,512 controls). Detailed lifetime job histories were elicited and a team of hygienists and chemists evaluated the evidence of exposure to a host of occupational substances, including CB. Lung cancer risk was analyzed in relation to each exposure, adjusting for several potential confounders, including smoking. Subjects with reported occupational exposure to CB, TiO2, industrial talc and cosmetic talc did not experience any detectable excess risk of lung cancer.

Overall, as a result of these detailed investigations, no causative link of CB exposure and cancer risk in humans has been demonstrated. This view is consistent with the IARC evaluation in 2006. The newer US study (Dell et al., 2015) not available to the IARC 2006 working group, also supports the lack of an excess lung cancer risk among CB production workers.

D. Workers exposed to Toner and Titanium dioxide: No lung cancer excess risk in workers

Similar results have been observed with other particles, such as toner and TiO2. Carbon black is used in the production of toner. Some laser printers and photocopiers use toner, which commonly contains carbon black mixed with a heat sensitive polymer. These products are ubiquitous in businesses and homes all over the world. The purpose of the information below is to summarize studies of the toner industry in which carbon black exposure was measured, assessed, or discussed.

As with coal miners, no lung cancer excess risks were found in large cohorts of toner-exposed workers. A large retrospective study of mortality risks of 33,671 employees occupationally exposed to toner was conducted (Abraham et al., 2010). The exposed group included employees involved in the manufacturing of toner and customer service engineers who serviced copiers in the field. All-cause SMRs for toner-exposed populations were 0.65 and 0.84 for white men and women respectively. SMRs for all cancers including lung cancer were lower than 1.0. There was no evidence that toner exposure increased the risk of all-cause mortality or cause-spe¬cific mortality for the 23 categories of death analyzed. No evidence of adverse effects on lung function or chest films was noted; no evidence of excessive inflammatory, allergic, or oxidative stress reaction was present in the toner-handling workers as compared to the non-specifically exposed workers (1504

male workers in a Japanese toner and photocopier manufacturing company, means of personal 8h respirable dust concentrations spanned from 0.012 mg/m3 in toner manufacturing to 0.989 mg/m3 in toner and photocopier recycling) (Kitamura et al., 2014).

No lung cancer excess risk was found in studies of TiO2-exposed workers. A multi-center occupational epidemiology study was performed in Europe that enrolled 15,017 workers long-term exposure to TiO2 (Boffetta et al., 2004). Four US production plants with a total of 4,241 exposed workers were studied (Fryzek et al., 2003).

The results of Kuempel et al., 2009 showed that the rat findings are difficult to rely on when the toxicological effects of PSP dust in humans are to be estimated in quantitative terms. Kuempel et al., 2009 commented on a comparison of rat-based risk estimates (MLE, maximum likelihood estimates) by translational toxicology and epidemiological risk assessments: "Regarding the magnitude of the excess risk estimates, the rat-based MLEs were clearly higher than the human-based estimate for coal dust (which was negative); however, the rat-based estimates (MLEs and 95% UCLs) did not exceed the 95% UCL from the human study. For carbon black, the rat-based excess risk estimates exceeded those from the human study, but the differences were not statistically significant. For titanium dioxide, the rat-based excess risk estimates (MLE and 95% UCL) were lower than the 95% UCL of the human studies, although the MLE from Fryzek et al., was negative" (Kuempel et al., 2009). For coal mine dust and carbon black these authors found that the rat estimates are in excess in comparison to the humans. Because of statistical imprecision, such a statement could not be derived for TiO2 but the authors stated that the epidemiological findings on TiO2 were negative.

In summary, no causative link between exposure to well-investigated respirable PSPs (including some nano-structured dusts), such as coal mine dust, TiO2, toner or CB, and an excess in lung cancer risk in humans has been demonstrated.
E. Summary: Weight of evidence assessment of epidemiology literature
Overall, well-conducted epidemiology studies of workers exposed to PSPs, including CB, coal and TiO2 do not indicate an increased risk of lung cancer. The rat inhalation studies in which female rats-but not male rats, mice, guinea pigs, hamsters or monkeys develop lung cancer are not valid for predicting lung cancer in humans. It is our considered view that the overwhelming evidence from well-conducted occupational epidemiological investigations on workers exposed to a range on PSPs, including carbon black, TiO2 and coal mine dust, are adequate, reliable and representative human data, and provide, "strong evidence that the mechanism of tumour formation in the female rat is not relevant for humans". Therefore, in a weight of evidence assessment taking into consideration, epidemiological findings, experimental interspecies differences, mode of action findings and accepting that lung tumours induced by PSPs such as TiO2, are unique to the rat and not predictive for humans, the classification for carcinogenesis (CAT 1B) proposed in the ANSES report is not defensible.

IV. Conclusions
The ANSES document does not provide reasonably convincing scientific evidence for the use of rat inhalation studies to classify PSPs (including TiO2) as presumed (CAT 1B) or even suspected (CAT 2) human carcinogens. The failure of the ANSES CLH report to directly assess the extensive human epidemiology literature of workers exposed to PSPs in conjunction with the rat results is a major scientific shortcoming and makes it unreliable for the purposes of human risk assessment and classification. In our opinion, a thorough examination of the entire relevant scientific database leads to the conclusion that for TiO2, no CLP classification for carcinogenicity is appropriate.

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VI. Appendix
A. Comments on the GBS document of the German MAK Commission
ANSES suggested a 1B carcinogenicity classification of TiO2 (carcinogenic to animals) based on the overload phenomenon in rats, also referring to the German MAK document on GBS (granular biopersistent particles without known specific toxicology) which states that all GBS are carcinogenic to animals and humans, including titanium dioxide (Hartwig 2014).

Apparently, ANSES agrees completely with the description of MAK's GBS approach as given in Morfeld et al., (2015a) on page 2 and 3. They used virtually an identical wording in their conclusion on page 60, although the report did not refer to Morfeld et al., (2015a). It is an important omission that the critical review of Morfeld et al., 2015a was not cited and discussed by ANSES in their CLH report on TiO2. We add that ANSES presented no scientific discussion of the MAK approach. MAK's GBS document was simply cited by ANSES as evidence in favour of a cancer classification of TiO2.

The MAK Commission developed in their GBS document (Hartwig 2014) a new approach and translated findings from rat overload experiments quantitatively into HECs (human equivalent concentrations) to derive an OEL (occupational limit value) for GBS. Importantly, the MAK Commission also performed a cancer classification of GBS that depends on the reliability of the translational toxicology models applied. The MAK Commission stated: "… the data obtained in test animals on the potential carcinogenicity of particles can be applied to humans if species-specific conditions (anatomy and histology of the respiratory tract) are taken into account" (Hartwig 2014, p. 19) (see the MAK Committee's manifesto on the carcinogenicity classification in Hartwig 2014, p. 63.)

Morfeld et al., 2015a commented: "This new MAK approach is a substantial departure from principles that have been used for many years in including results of human studies, most notably epidemiological findings. To rely so heavily on translational toxicology models only, the new approach must be transparent, consistent, and evidence-based". In their review, the authors examined the scientific assumptions used by the MAK Commission.

Briefly, Morfeld et al., (2015a) emphasized that this classification depends on the reliability of the translational toxicology models. Moreover, goodness of models requires the correctness of input data. We adopt the comments by Prof. Hartwig (Hartwig 2015), chair of the MAK Commission, on Morfeld et al., (2015a) and the reply from the authors (Morfeld et al., 2015b) to Prof. Hartwig. Below we want to summarize and highlight the discussion about the correctness of models and input data with respect to the MAK's recommendation. It is a further and important omission that ANSES did not refer to this published exchange about the scientific validity of MAK's GBS approach.

Morfeld et al., 2015a concluded: "The calculations described in the MAK document (Hartwig 2014) on GBS are based on a number of incorrect assumptions and calculations related to the use of lung surface area, particle clearance rates and deposition fractions among others which are shortcomings that affect both translational overload models (Model A and Model B) used to derive the HEC for GBS. The methods applied do not reflect state of the art techniques and cannot be independently replicated since the hyper link cited by the MAK Commission no longer leads to the program version the Commission and Pauluhn (2011) applied (MPPD 2.0). In Pauluhn (2011), calculations were based on a Fortran program that is not publicly available. More importantly, the approaches are inconsistent as they rely on conflicting assumptions. The resulting errors are so large that

the MAK Commission's suggestion (Hartwig 2014) as to how to translate inflammation/overload findings from rats to humans is unreliable and the OEL proposal is unsubstantiated. This also affects the justification of the MAK Commission's cancer classification which is related to humans (Carcinogen Category 4) but based on overload inhalation experiments with rats. This classification relied on the validity of the proposed translational overload models."

Thus, it is inappropriate to cite MAK's GBS approach in ANSES report as evidence for a cancer classification of TiO2 without considering the detailed review by Morfeld et al., 2015a and the letter exchange published (Hartwig 2015, Morfeld 2015b). The GBS approach should be discussed by ANSES in detail and evaluated on the background of the raised criticisms or the passage about GBS should be dropped.

In the following, we like to highlight just a few aspects of MAK's translational toxicology models that should be important in any scientific evaluation of the MAK's GBS approach. We do not repeat the more general problems related to e.g., the AOP (adverse outcome pathway) analysis and particle surface area metric and refer to Morfeld 2015a, Morfeld 2015b for any details.

Proper input data and consistent mathematical structures are critical for goodness of models

1) To derive an exposure limit (MAK value), the MAK commission applied two different models. One approach based on retained particle mass per alveolar surface area (Model A) and another on retained particle volume per macrophage pool volume (Model B).

Model A: wrong density correction

The MAK Commission considered that in Model A "the particle clearance and the retained particle dose is not dependent on the particle density per se but on the particle volume (Density = mass/volume)." Interestingly, the MAK commission applied alveolar clearance rates invariant of "density" and "volume" (given the same species), and used the identical clearance rates for substances with very different densities in Model A. This application by the MAK Commission is contradictory to Model A as published and consequently the derivate is unreliable.

Model B: wrong rule of three
Model B used by MAK is based on the second derivations of Pauluhn (2011). However, the units were confused and the standardization by rat lung mass or rat body weight is varying and inconsistent (Morfeld et al., 2015). Hartwig (2015) did not address this important error in their reply (wrong application of the rule of three).

2) Outdated and not available
The MAK Commission employed the MMPD model Version 2.0 to calculate the particle dose deposited in the lung. In fact, this program version is outdated and not available under the hyperlinks provided by the MAK Commission. Hence, the calculation is not reproducible.

3) Even not reproducible with outdated program
The MAK commission supposedly asked two experts to cross check with Version 2.0, the correctness of the deposition fraction used in Model A. Whereas Morfeld et al., 2015 criticized that the deposition fraction as used in Model B – not Model A - was unjustified. Morfeld et al., 2015 showed that the deposition fraction used in Model B cannot be reproduced applying the input data published in Hartwig 2014, neither with the current

nor with the outdated MPPD program version.

4) Alveolar lung surface area
The MAK Commission used 57.22 m2 for the human alveolar surface area. This should represent a normal exhalation value. However, the background of this value could not be substantiated. Instead, data from Gehr et al., (1978) should have been used which are referred to as the current gold standard. These authors reported a surface area of 144 m2 at maximum inhalation. Furthermore, we have to note that the main discussion does not deal with the absolute value of the lung surface area but the ratio of lung surface areas between humans and rats. Because the lung surface area ratio is used in Model A to translate findings from experimental rats to workers, we have to consider both, rat and human surface area data. To be noted, the methods used to determine the surface areas both for humans and for rats should be same, in order to derive a reliable ratio. Furthermore, an unbiased estimate of the human/rat ratio based on state-of-art methods is 349, but not 193 as applied in (Hartwig, 2014).

5) Average clearance half-time
An average clearance half-time of 400 days was applied for humans by the MAK Commission in Models A and B, which corresponds to the clearance half time from the alveolar to bronchial region according to Gregoratto (2012), a state-of-the-art paper. In contrast, a half time of about 255 days is expected from the alveolar compartment considering both, the clearance into the bronchial region and into the interstitium, again according to Gregoratto (2012). We have to consider that MAK's Model A and B limit all adverse effects to an interaction of deposited dust with structures/cells within the alveolar compartment. Thus, 255 days should be used in calculations based on Models A and B, instead of 400 days.

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B. Comments on the "Respiratory disease mortality among US coal miners; results after 37 years of follow-up" by Graber et al., 2014

The ECHA draft guidance on information requirements and Chemical Safety Assessment Appendix R7-1 Recommendations for nanomaterials" mentioned a coal miner study, not discussed in the ANSES report. On page 10, they say that the overload has relevance for humans because of a new coal miner study from the US (Graber et al., 2014). To be more precise, ECHA reported on the general overload discussion by Valberg et al., 2009 (P. Valberg, J. Bruch, RJ McCunney "Are rat results from intratracheal instillation of 19 granular dusts a reliable basis for predicting cancer risk?"," Regulatory Toxicology and Pharmacology, vol. 54, no. 1, p. 72–83, 2009) and commented on page 10 on Valberg et al., 2009 as follows:

"They argued that the response of rats to PSP lung overload is stereotyped and unique to that species and pointed towards human exposure to justify this. Specifically, they noted that workers historically exposed to potentially lung-overloading burdens of inhaled dust (e.g., coal workers, underground miners using diesel equipment) do not exhibit an established lung-cancer excess despite the potential for lung overload. However, a recent epidemiological study evaluating the underlying cause of death for 9033 underground coal miners from 31 US mines after 37 years of follow-up (Graber et al., 2014), found a significant relationship between coal mine dust exposure and lung cancer mortality. Hence, the data obtained from rats may still be useful to predict the effects in humans."

Thus, a critical discussion of Graber et al., 2014 is necessary.

Background on Graber et al., 2014

The Graber et al., (2014) is an updated US coal miner mortality study with an extended follow-up for 37 years. The study used cumulative coal mine dust exposure to examine exposure-response associations. Negative findings were reported in coal miners with respect to lung cancer from earlier studies. In contrast, the study of Graber et al., (2014) found "an overall excess of lung cancer mortality (SMR = 1.08; 95% CI 1.00 to 1.18) and a significant association with cumulative coal mine dust exposure and lung cancer in the last decade of follow-up 2000-2007". The limitations of the exposure assessment and analysis methods are noted in their discussion.

We reviewed the Graber et al., (2014) report, in particular the association between coal mine dust and lung cancer mortality, and we like to offer our view on it. We adopted the viewpoints in two Letters to the Editor (Morfeld 2014; Taeger et al., 2014).

Included below are our comments on the exposure assessment and analysis methodology, as well as overall findings and conclusion.

Comments on the exposure assessment

The study suffers from an incomplete assessment of occupational histories in coal mine workers. There was no information on jobs held after 1969/1971, and no end date of working as a coal miner for 16.2% of cohort members. In addition, translation of limited environmental measurement values into individual exposure data is another source of inaccuracy.

(1) Cumulative coal mine dust exposure was defined as the sum of the products of each job-specific dust concentration and the duration of time worked at that job. Some exposure assessments were based on some measurements collected during environmental surveys at certain US mines by the Bureau of Mines between 1968 and 1969. In addition, the exact duration of specific jobs held could not be derived from the incomplete job histories. To overcome this sparse data situation in this study, the strong assumption was made that the jobs of the miners and the level of exposure have not changed after study enrolment.
Hence, only a crude assessment of exposure to coal mine dust up to the start of follow-up was possible. Consequently, the risk estimates based on the mean cumulative coal mine dust exposure are questionable.
Crystalline silica concentration data suffered from additional limitations because measurements were available only after 1981 but had to be allocated to jobs held before 1969/1971. This may have lead a potential upward bias of risk estimates assuming that exposure to quartz decreased with time.

(2) Due to the lack of entry and end dates of jobs, potentially different employment patterns could not be considered and the exposure could not be handled in a time-dependent manner. Thus, the results suffer from the limitation due to the Healthy Worker Survivor Effect (models that adjust for time since last employment do not solve this problem).

(3) For the reason of lacking of end dates of employment, lagging or lugging time analysis was not possible in this study.

(4) Sensitivity analysis examined the sub-cohort members with known end date working as a coal miner. The mean cumulative coal mine dust and respirable silica dust exposure estimates were 83.0 mg/m3-year (SD =41.3) and 4.1 mg/m3-years (SD=1.8), while the mean values of the whole cohort were 64.6 (SD = 46.4), and 2.6 (SD = 1.0), respectively. However, the authors argued that “the coefficients for the exposure-response relationships with each of the outcomes were statistically similar for the extended compared with the original estimates”. Obviously, the distribution of the cumulative exposure values differs between the sub-cohort and the whole cohort.

Comments on Analysis Methodology

The authors performed external and internal analyses, which both contain errors.

(1) As a result from external analysis, the overall lung cancer SMR was slightly elevated (SMR=1.08, 95% CI: 1.00 -1.18), disregarding the fact that a higher proportion of smokers (current smoker: 54%) at the start of follow-up in 1969/1971 than that of the US male population in 1970 (44.1%) [Morfeld 2014]. The authors used age-, calendar-, sex-, and race-specific mortality ratios, without adjusting for smoking status. Axelson's approach is, however, available to adjust for the confounding effect of smoking.

Referring to the approach of Axelson (1978), we calculated the correction factor considering the compositions of non-smokers (25%), former smokers (30%), and current

smokers (45%) in the reference population of US male in 1970, and compositions of non-smokers (20.4%), former smokers (25.6%), and current smokers (54.0%) of the study population. The correction factor might lie between 1.2 and 1.6. Even a 10% correction would reduce the tentative SMR below unity.

(2) Taeger et al., pointed out in their Letter to the editor that SMRs differed considerably between regions, in particular for lung cancer. They suggested to use regional rates for SMR calculation, and combined the results finally. The authors acknowledged that the suggested method would be more reasonable.

(3) The authors emphasised that the results from the internal comparison should be focused on. In Table 4 of Graber et al., the HRs of cumulative coal mine dust and respirable silica per mg/m3-year were falsely calculated. A B-coefficient of 0.1271 would yield a HR of 1.136, and B-coefficient = 0.0191 yields HR = 1.02, as pointed out by Taeger et al., in their letter as well. Hence, both results in this respect are obviously erroneous, which has NOT been considered in their Erratum, which was published in October 2014.

(4) In addition, Table 4 demonstrated apparently that smoking, either in qualitative or in quantitative assessment, was associated with an increased risk of lung cancer. Therefore, the conclusion of the authors that "Our findings support …… from malignant and non-malignant respiratory diseases even in the absence of smoking" is not in line with the results presented. The conclusion should be restricted to mortality from COPD.

(5) Table 5: a significant association between cumulative exposure to coal mine dust and lung cancer was shown only for the time period 2000 – 2007. There was substantial difference of risk estimates, both in magnitudes and direction, across the time periods. Therefore, it is of interest to see the distribution of the cumulative exposure according to time period. Furthermore, the definition of time periods with differing length (20, 10, and 8 years) seemed to be arbitrary.

Additional errors are in the Abstract regarding the published confidence limits as pointed out by Taeger et al., (2014). The authors acknowledged "some transcription errors" und revised them in Erratum.

Comments on the overall findings and conclusions

(1) The most recent coal miner study in US (Graber et al., 2014) observed slightly excess mortality for lung cancer (SMR = 1.08; 95% CI: 1.00 – 1.18), comparing with the general population. SMR as risk measure has its limitation due to the comparability with the reference population, here in particular with respect to smoking status. Despite the higher prevalence of active smokers in the study population, the authors did not adjust for the confounding effect of smoking. Axelson's approach can be applied to adjust for different composition of smoker and non-smokers in the study population. The tentative SMR would reduce substantially below unity.

(2) The authors emphasize that the major findings of the study are based predominantly on internal comparison. The quantitative exposure-response analysis showed significant association between coal mine dust exposure and lung cancer. The HRs from the Cox regression models are, however, obviously erroneous. Nevertheless, the results are not revised in their Erratum.

(3) The study has some severe inherent shortcomings. Firstly, only a crude exposure assessment was possible, i.e., translations from hygiene measurements to individual

exposure is inaccurate. Secondly, the job duration of a specific job activity was not known for many miners. Consequently, the cumulative exposure measure must be inaccurate and the risk estimate for cumulative exposure per unit is potentially biased.

(4) All follow-up periods from 1970 to 1999 showed no association between coal mine dust exposure and lung cancer, except that of 2000 to 2007. This might raise the question if coal mine dust may act as a late stage lung carcinogen. In an extended follow-up of the UK study of Carbon Black (CB), Sorahan and Harrington (2007) applied a novel exposure metric ("lugging") to study if the elevated SMRs of decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative exposure.
Nevertheless, the study of Graber et al., (2014) does not provide the adequate information to address this issue analytically.

The study relies on smoking information collected only at the start of follow-up. The models are unable to adjust for smoking habits after leaving work. Note that current smokers smoked less when working as a coal miner than current smokers in the US male population (prevalence of smoking more than 25 cigarettes per day: 12.4% among US coal miners vs. 28.0 % in the US male population). This difference is probably caused by prohibition of smoking when working underground. It is plausible that smoking coal miners have increased their intensity of smoking after cessation of work underground and that this may have caused an increase in lung cancer mortality during the last follow-up period when most coal miners of the cohort have already stopped working underground [see the discussion of this issue in Miller and MacCalman 2010].

The authors stated in their reply to a Letter to the Editor (Morfeld 2014): "We agree with Dr. Morfeld, and stated in our article, that the British study of coal miners (Miller and MacCalman 2010) had better exposure data than our study". It is important to note that the British study did not find association between coal mining and lung cancer risk, neither when compared to the general population or in internal analyses of the effect of coal mine dust exposure (Miller and MacCalman 2010). The same is true for all other analyses published on the US study (Attfield and Kuempel 2008). Similar results were found in Germany, based on a detailed and time-dependent exposure assessment in an analysis of lung cancer mortality and incidence data (Morfeld et al., 2002, Morfeld et al., 2004, Morfeld et al., 2007).

It is not a reliable "weight of evidence approach" to base all conclusions about coal miners cancer risk on the study of Graber et al., 2015 alone while ignoring the better UK study and the evidence from other countries. In addition, the important limitations of Graber et al., (2015) should be addressed as outlined in two Letters to the Editor (Morfeld 2014, Taeger et al., 2014) and a recent review (Morfeld et al., 2015).

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ECHA note – A non confidential attachment was submitted with the comment above. ANSES Proposed Classification of TiO2 - Comments by CB4REACH - 14 July 2016 - FINAL.pdf

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Carbon Black For REACH Consortium	BehalfOfAnOrganisation	319

Comment received

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I. Introduction
A. Background/interest in topic; scientific advisory group's perspective of a substance also considered a PSP: carbon black
The Carbon Black for REACH Consortium (CB4REACH) offers comments on the CLH report, submitted by ANSES and proposing a harmonised classification and labelling for Titanium dioxide (TiO2) for the carcinogenicity endpoint (ECHA 2016). Scientific and medical experts of the Scientific Advisory Group (SAG) of the International Carbon Black Association (ICBA) developed these comments on behalf of the CB4REACH Consortium. As members of ICBA's SAG, we have overseen and conducted numerous peer-reviewed epidemiology, toxicology and industrial hygiene studies related to carbon black (CB), a substance often described - like TiO2- as a poorly soluble particle (PSP).

We offer these comments as many of the scientific issues raised in the ANSES CLH report are based, not only on TiO2, but on other respirable PSPs, including CB, a substance which has been extensively investigated, through CB-exposed production worker studies for mortality and morbidity endpoints as well as through many informative rodent inhalation studies and in vitro investigations.

We specifically comment on three key aspects, namely:

(1) ANSES's evaluation of the significance to humans of lung overload endpoints in laboratory rodents; and in particular lung cancer in the rat; and

(2) An evaluation of the epidemiology literature of coal miners as it relates to lung overload in rats. In general, ANSES concludes that rat inhalation studies in which lung overload is associated with cancer should be used in human risk assessment, most notably for risk of lung cancer. The ANSES report, however, ignores the vast literature of mortality studies of TiO2, coal miners and CB production workers, in which lung cancer risk was not elevated, even among the most heavily exposed coal miners who developed Coal Workers pneumoconiosis (CWP) or in the TiO2 and CB production workers.

(3) The overall evidence base does not meet the CLP criteria for classification for carcinogenicity of Carc. Cat 1B – H350i as proposed in the ANSES draft document.
II. Commentary regarding ANSES's assessment of lung overload
A. ANSES: Implications of lung overload in laboratory rats for human health risk assessment.
In the ANSES TiO2 document, it is stated: "This CLH report therefore focuses on carcinogenicity of TiO2. Indeed, because the carcinogenic mode of action of TiO2 seems to be rather due to inflammatory process and oxidative stress, it is believed that biopersistence and solubility are relevant to explain this toxicological effect….Indeed TiO2 in all these combination is considered to behave in the same way as other poorly soluble low toxicity particles (e.g. coal dust, diesel exhaust particulates, toner …). This statement does not preclude that some parameters (in particular shape and coating) might also lead to a more potent carcinogenicity or to other specific lesions via a specific mode of action. The proposal presented below is based on data considered sufficient by MSCA-FR to propose a general entry for classification of TiO2 for Carcinogenicity by inhalation. In case new data is available, the entry may be modified upon submission of these data by the registrant."

Comment:
The above reasoning by ANSES is that rat lung tumours, seen with TiO2 and other PSPs (such as CB), is predictive of human risk. However, the evidence from other rodent species (such as mice and hamsters) and a wealth of relevant and well-conducted epidemiological investigations, not addressed in the ANSES report, strongly supports the contention that the lung tumour response, seen in rats, is unique to that species under overload conditions and related to an exaggerated inflammatory response causing a secondary (non-direct genotoxic) carcinogenic mode of action (Morfeld et al., 2015; ECETOC 2013).

In their report, ANSES justifies its carcinogenicity classification of TiO2 based on studies of laboratory rats. In the section on "Carcinogenicity", the report states: "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable,"

Comment:
However, the ANSES report provides no detail or epidemiological evidence from the many available studies to support this broad and dismissive conclusion. We find it totally inappropriate to dismiss such a large body of well-conducted peer-reviewed investigations into occupational exposure to TiO2 and other relevant occupational studies with PSPs.

The ANSES report then describes the results of the animal studies in more detail.

"In experimental animal studies, lung tumours were reported after inhalation or intra-tracheal administration of in rats in an overload context. Overload is defined by an impairment of normal pulmonary clearance due to high accumulation of particles. Although inter-species variability was found in particle retention, the overload concept is relevant for humans, and in particular for workers exposed to high dust concentrations.

Comment:
To support this contention, it would be appropriate for ANSES to define what they mean by "high dust concentrations" and to define criteria for overload.

Furthermore, it appears that lung retention and chronic pulmonary inflammation occurring in humans are consistent with the findings in rats."

Comment:
We note that this latter statement in the ANSES report is inconsistent with the scientific literature (described later.)

"Although benign lung tumours (bronchioalveolar adenomas) were observed in both sexes, malignant tumours (squamous cell carcinomas and bronchioalveolar adenocarcinomas) were only reported in female rats… Based on these effects, IARC (2006) concluded that there is sufficient evidence that TiO2 is carcinogenic in animals.

Although the full mode of action is still unclear, an inflammatory process and indirect genotoxic effect through ROS production seems to be the major mechanism to explain the effects induced by TiO2. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO2 particles. However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO2 was found in the cell nucleus in various in vitro and in vivo studies".

Comment:
We feel that it is unhelpful for ANSES to state that at "a genotoxic effect by direct interaction with DNA cannot be excluded…" as clearly, one cannot ever prove a negative and the overwhelming in vitro and in vivo studies demonstrate that TiO2 is not directly genotoxic.

The proposed mechanism is already described for other substances such as aluminium oxide, insoluble nickel salts and iron oxides, acting as poorly soluble low toxicity particles, which elicit lung tumours in rats following prolonged exposure at sufficiently high concentrations.

Therefore, classification as Carc. Cat 1B – H350i is justified for TiO2 considering the increase of both malignant and benign lung tumours in one species, reported in two studies by inhalation and two studies by instillation after exposure to TiO2."

Comment:
Our considered view is that if one used a weight of evidence approach, as recommended by ECHA in its Guidance on information requirements and chemical safety assessment - Chapter R.4: Evaluation of available information, and envisioned by the CLP regulation (section 1.1.1 of Regulation (EC) No 1272/2008), and included epidemiological studies, experimental interspecies differences and mode of action findings and accepted that lung tumours induced by PSPs such as TiO2, were unique to the rat and not predictive for humans, then no classification would seem far more appropriate and consistent with the

science base.

ANSES mentioned the GBS approach of the German MAK Commission in favour of a cancer classification of TiO2. We draw attention to the review by Morfeld et al., 2015 that discusses the scientific shortcomings and lack of reproducibility of the MAK approach and to the fact that these limitations of the GBS approach were not discussed by ANSES. We refer readers to Appendix A for details.
B. Carbon Black for REACH Consortium's Response to ANSES commentary on use of rat overload results data for human risk assessment
B1. Mechanism of the Rat Lung Response to Particle Overload
CB is a PSP similar to TiO2; therefore it is useful to evaluate pulmonary studies on CB as the results are directly relevant to TiO2. In numerous studies, rodents, particularly rats, have been exposed by inhalation to CB. Based on the results from these studies a number of conclusions may be drawn.

First, prolonged inhalation of high levels of CB causes delayed pulmonary clearance and marked retention of particles. This phenomenon is described as "lung overload" (IARC 1996; Mauderly, 1996) and is common for a range of respirable insoluble dusts of low toxicity (PSPs). The sequelae to these high lung burdens in rats include inflammation, which leads to a range of changes in pro- and anti-inflammatory biochemical parameters (found in bronchoalveolar lavage fluid), epithelial hyperplasia, and pulmonary fibrosis.

Second, rats are more sensitive to the effects of CB overload than other species; with female rats having more pronounced reactions than male rats (ILSI, 2000). In long-term studies, only female rats were prone to a significant increase in the development of lung tumours. The lowest CB concentration used in a chronic inhalation study where lung tumours were induced was 2.5 mg/m3, with rats being exposed for 16 hours/day, 5 days/week for 2 years (Nikula et al., 1995). However, mice exposed to 11.6 mg/m3 CB for 18 hours/day, 5 days/week for 13.5 months and observed for a further 9.5 months did not exhibit an increase in lung tumours (Heinrich et al., 1995). In primates (Nikula et al., 1997) and in humans (Mauderly 1996), there are clear differences in particle deposition, clearance patterns, and tissue reactions, when compared to rats. These differences underline the uniqueness of the rat tumour development under conditions of lung overload and raise questions as to the validity of interspecies extrapolations of particle effects from rats to humans.

Third, results from genotoxicity studies suggest a direct association of mutation with inflammation and its sequelae in rat lung tumour development. Lung inflammation leads to the production of reactive oxygen species, and these mutational lesions seen in the ex vivo hprt assay can be prevented by experimental treatment with antioxidants (Driscoll et al., 1997). This study demonstrated that the increase in mutation frequency is caused by oxidative damage alone, typical of a secondary genotoxic mechanism.

The prevailing scientific consensus is that rat lung tumours induced by inert, PSPs, such as CB and TiO2, arise out of a background of chronic and persistent inflammatory changes; the corollary being that if these changes are avoided, then the tumours will not occur (ECETOC 2013). In this respect, the studies of Driscoll et al., (1996) are of particular relevance because exposure to 1.1 mg/m3 of respirable CB particles did not evoke inflammatory or mutational changes to female rats. A no observed adverse effect level (NOAEL) of 1 mg/m3 (respirable) CB is supported by other rodent findings by Oberdoerster, Driscoll, and colleagues (Carter et al., 2006, Elder et al., 2005; Driscoll et al., 2002; ILSI, 2000).

To summarize, the major rodent interspecies differences in lung responses to inhaled CB

particles are:

a) the pulmonary clearance of CB particles was significantly faster in hamsters vs. rats or mice;
b) exposures to higher concentrations of CB produced particle overload in the lungs of both rats and mice;
c) the pulmonary cellular and tissue responses to particle overload were different in the rats when compared to similarly exposed mice – i.e., rats developed greater and sustained lung inflammatory responses and significantly more intensive epithelial and fibro-proliferative responses.
B2. Pulmonary Response in Mammalian Species Other Than Rodents
In studies reported by Nikula et al., (1997, 2001), it is proposed that the intrapulmonary particle retention patterns and tissue reactions in rats may not be predictive of pulmonary retention patterns and tissue responses in either primates or humans. Male cynomolgus monkeys and F344 rats were exposed for 7 hours/day, 5 days/week for 24 months to diesel exhaust (2 mg/m3), coal dust (2 mg/m3), or diesel exhaust and coal dust combined (1 mg/m3 each) and were subsequently examined histopathologically (Nikula et al., 1997). In all exposed groups, monkeys retained a similar amount or more particulate material in the lungs than did rats. Rats retained a greater proportion of the particulate material in the alveolar ducts and alveoli, whereas monkeys retained a greater proportion of particulate material in the interstitium. Rats, but not monkeys, had significant alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses to the retained particles.

In a subsequent study, Nikula et al., (2001) evaluated the influence of exposure concentration on the distribution of particulate material within the lungs of rats and humans. In this study the investigators used morphometric methods to assess the influence of exposure concentration on particle retention by evaluating histological lung sections from rats and humans. The rats had been exposed for 24 months to diesel exhaust at 0.35, 3.5, or 7.0 mg/m3. The human subject groups included: 1) non-smokers who did not work as miners; 2) non-smoking coal miners who worked under the current standard of 2 mg dust/m3 for 10-20 years; and 3) non-smoking coal miners who worked under the former standard of <10 mg dust/m3 for 33 to 50 years. The distribution of retained particles within the lung compartments was markedly different between species. In all three groups of rats, 82 to 85% of the retained particulate material was located in the alveolar and alveolar duct lumens, primarily in macrophages. In humans, 57, 68, and 91% of the retained particulate material, respectively, was located in the interstitium of the lung in the three aforementioned study groups. The authors concluded: "These results show that chronically inhaled diesel soot is retained predominantly in the airspaces of rats over a wide range of exposures, whereas in humans, chronically inhaled particulate material is retained primarily in the interstitium. In humans, the percentage of particles in the interstitium is increased with increasing dose (exposure concentration, years of exposure, and/or lung burden). This difference in distribution may bring different lung cells into contact with the retained particles or particle-containing macrophages in rats and humans and, therefore, may account for differences in species response to inhaled particles."

A comprehensive review on translational toxicology focusing on PSP exposure and on CB, as one example, was published by Morfeld et al., in 2015.
B3. Species-specific response to poorly soluble particles
It is possible to explore the species differences using the Mode of Action, the AOP (Adverse Outcome Pathway) and events at the molecular level to better refine the way translational toxicology is used to exchange experimental findings between rodent species, primates and human responses to PSPs. From the wealth of available data, it

seems too simplistic to simply assume that what occurs in the rats can be assumed to occur in humans without carefully taking into account both critical toxicokinetic and toxicodynamic differences. This means that we have to take into account the totality of the available information at the anatomical, physiological, cellular and molecular level in a reliable translational exercise. Rats have been consistently shown to have a more sensitive response to the chronic inhalation of respirable particles compared to other species, and a unique response in relation to lung cancer. The species-specific differences in responses are summarized in Table 1. Thus, in agreement with ECETOC (ECETOC, 2013), mechanistic data are available to overcome the default statement made by the ILSI panel in 2000 (ILSI, 2000) and cited in Kuempel et al., 2014. This conclusion is consistent with findings from studies on humans.

Table 1: Interspecies lung responses a following long-term or chronic inhalation exposure to granular biopersistent substances (=PSPs)

Species	Rat	Mouse	Hamster	Primate/Human
Likelihood for developing particle overload (slow lung clearance)	+++	+++	+	Not determined*
Alveolar macrophage participation	Active (accumulation in alveolar ducts)	Active (accumulation in alveolar ducts)	Extensive (rapid clearance)	Not as extensive (translocation to interstitial sites)
Pulmonary (neutrophilic) inflammation	+++	+++	+	+
Epithelial and interstitial cell proliferation	+++	+	(+)	(+)
Septal fibrosis	+++	+	(+)	(+)
Anatomical location of retained particulates	Primarily alveolar (some increased translocation at overload)	Primarily alveolar (some translocation at overload)	Rapid clearance	Primarily interstitial
Lung tumours following chronic exposure	Yes	No	No	No

a Severity low +, moderate ++, high +++, or questionable (+), reprinted with permission from [ECETOC 2013, p. 52]**

*This should be + (see page 53 in ECETOC 2013 because particle overload is typified by an impairment in alveolar particle clearance (see pages 1 and 4 in ECETOC 2013.

**There may be a variance of opinion about the extent/degree of some of the endpoints in the table (e.g., alveolar macrophage participation, septal fibrosis) and there is continuing research to refine these findings.

Variable responses, at the cellular and molecular levels, as well as regarding tumour development (defence systems) are seen in mice, hamster, rats, and primates following particle exposure. It is thus important to ascertain how these models perform, in a translational exercise between these three and possibly other species, to verify the "species independent" assumption.

B4. Differences in Broncho alveolar lavage (BAL) findings in rats and humans

BAL studies in humans are consistent with epidemiological results of workers. BAL is a widely used clinical diagnostic study in the evaluation of lung disorders, particularly in the differentiation of interstitial lung diseases (ILD). In light of the emphasis given in the ANSES CLP report and also by others such as the MAK Commission (Hartwig et al., 2012), to data from rat experiments, it would be valuable to determine whether corresponding biomarkers can be identified in human BAL fluid of dust-exposed people.

BALF on coal workers were assessed for their cellular profile (Kayacan et al., 2003; Xing et al., 2006; Vallyathan et al., 2000; Vanhee et al., 1994; and Vanhee et al., 1995). Epidemiological data do not provide convincing support for an increased lung cancer risk

in people exposed to high dust levels, such as coal miners. Epidemiological findings contrast with the results of experimental studies on rats, in which at higher exposure levels, excess lung tumours were detected. Chronic inflammation is the underlying mechanism, which causes secondary genotoxic events by oxidative damage due to inflammatory cells.

Groups of miners with different stages of coal workers' pneumoconiosis (CWP) were compared (posterior-anterior chest radiographs, ILO resp. Chinese x-ray staging of CWP). No increased counts for PMNs were detected in asymptomatic miners and in miners with low grades of simple pneumoconiosis, i.e., CWP ≤ 1/1 (Kayacan et al., 2003; Xing et al., 2006)]. One group of miners with simple pneumoconiosis showed an elevation of the neutrophil percentages in the BALF in comparison to controls (Vanhee et al., 1994). In contrast, a second group studied by the same researchers showed almost the same average neutrophil percentage as reported for controls Vanhee et al., 1995)].

Xing et al., 2006, studied biomarkers in the BALFs of coal mine workers: 14 active underground miners without CWP, 21 workers with CWP 0/1, and 13 no longer exposed workers after cessation of exposure with CWP 1/1. None of the groups showed elevated neutrophils numbers (PMNs). However, other biomarkers in the BALF of the coal workers were clearly changed; for instance, markers of the epithelial reaction (pneumocyte type II): (a) increased surfactant lipids, (b) altered ratio of PG/PI (subgroups of lung surfactant: phosphatidyl glycerol PG, phosphatidyl initisol PI), (c) increased surfactant protein A. The elevated TNF alpha content in the BALF (d) stands for the effect of the phagocytosed particles on AM. Interestingly, the results on parameters (a, b, d) correspond to findings in dust-exposed rats, e.g., the increased surfactant lipids, the altered ratio of PG/PI, the elevation of TNF alpha (Adachi et al., 1989; Nehls et al., 1997; Seiler et al., 2001) It is worth mentioning that rats exposed to coal dust showed a significant increase of PMNs in the BALF (Donaldson et al., 1990).The investigations of Vanhee et al.,1995 identified different profiles of growth factors (PDGF, IGF1, TGF beta) in the BALF of coal miners according to the severity of x-ray changes. Further, in vitro and in vivo studies on human (BALF) alveolar macrophages from patients with different grades of pneumoconiosis clearly demonstrated the eminent role of the AM for the onset and development of the coal miners' lung disease. Mixed CS and coal dust exposures eventually trigger an aggressive form of pneumoconiosis and BALF pattern (Vallyathan et al., 2000) The miners´ individual working-lifetime exposures (n = 20) were estimated from this study, using work histories and airborne mine dust data. The quartz lung-burdens were calculated using a lung dosimetry model. The study showed that quartz, either as cumulative exposure or as calculated lung burden, was a highly significant predictor of PMN lung response. The cumulative coal dust exposure did not contribute to the prediction of PMNs (Kuempel et al., 2003)

An American Thoracic Society (ATS) clinical practice guideline on the utility of BALF cellular analysis summarized for CWP that BALF cell profiles, indicative of increased numbers of macrophages and elevated proportion of coal dust-laden macrophages, are suggestive of CWP or progressive massive fibrosis (PMF) (Meyer et al., 2012) The authors stated for silicosis that BALF profiles of silica-exposed workers and workers with silicosis are characterized by an excess in BALF macrophages and an increased silica particle burden of macrophages that is appreciable in non-smokers. Meyer et al., 2012, made no recommendations regarding the clinical utility for prognosis of CWP or PMF. The authors noted the prognostic value for silicosis that increased numbers of lymphocytes and neutrophils have been associated with progression to silicosis.

In conclusion, the prominent role given to the BALF-PMNs in relation to the particle lung exposure in rats does not correspond to BAL results in humans. Human data reflect a

significant role for the alveolar macrophages and type II pneumocytes in the development of dust induced interstitial lung diseases (ILDs) in humans, a role also played in rat studies (Rom et al., 1987). The PMNs, however, play a unique role in rat experiments, findings that do not appear to occur in high dust (PSP) exposed workers, such as coal miners. In conclusion, the human BAL biomarker studies corroborate the epidemiological findings.
B5. Summary of implications of lung overload in rats for human risk assessment
Although lung tumours are induced in rats when exposed to CB, it is generally acknowledged that these tumours are produced because of the lung overload phenomenon, a point noted in the ANSES CLP report as well. When exposed to a PSP such as CB in high concentrations, laboratory rats cannot adequately clear CB from their respiratory tract, so lung tumours are induced by a secondary non-genotoxic mechanism. Lung tumours were not observed in mice and hamsters under similar study conditions. The relevance of the rat tumour data to human risk assessment has been raised in an earlier review of the animal literature at a consensus conference of investigators (ILSI, 2000). An updated review by ECETOC (2013) also concluded that the rat represents a unique model with regard to lung neoplastic responses under conditions of lung overload: "The rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload." (ECETOC 2013).

In support of this above opinion, it should be noted that in ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2015), the issue of lung overload is mentioned under section 3.9.2.5.3, Mechanisms not relevant to humans (CLP Annex 1, 3.9.2.8.1 (e)) as "The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate". Also section 3.9.2.8.1 (e) of Annex 1 of CLP states that "Substance – induced species specific mechanisms of toxicity substance, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification". Further, section 3.6.1.1 of the CLP regulation states "Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans."

Section 1.1.1.4 of Annex 1 of the CLP regulation states that "Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data." It is our considered view that the overwhelming evidence from well-conducted occupational epidemiological investigations on workers exposed to a range on PSPs, including carbon black, TiO2 and coal mine dust, are adequate, reliable and representative human data, and provide, "strong evidence that the mechanism of tumour formation in the female rat is not relevant for humans". Therefore, in a weight of evidence assessment taking into consideration, epidemiological findings, experimental interspecies differences, mode of action findings and accepting that lung tumours induced by PSPs such as TiO2, are unique to the rat and not predictive for humans, the classification for carcinogenesis Cat 1B – H350i proposed in the ANSES report is not defensible.

The ANSES CLP report states: "It should be noted that, although it cannot be directly

transposable, there is a strong link between CLP and the IARC classification criteria since the definition of sufficient and limited evidence are part of the CLP criteria (guidance on the Application of the CLP criteria (version 4.1 – June 2015)).” It should be noted that, the evaluation by IARC of carbon black and TiO2 as possibly carcinogenic to humans – Group 2B, is based solely on the observation that rats develop lung tumours under condition of “lung overload” and was in contradiction to the numerous negative epidemiological studies conducted on workers exposed to these two substances (both evaluated as inadequate by the IARC Working Group). The reliability of lung tumours induced in rats by inert poorly soluble particles, such as carbon black, as a predictor of hazard to humans is uncertain. Overall, the epidemiological evidence from well-conducted investigations has not shown that exposure to carbon black or TiO2 has a carcinogenic potential for humans (See detailed commentary later in this report CB mortality studies. The arguments regarding the uniqueness of rats in developing lung cancers under conditions of lung overload with PSPs (including TiO2 and CB) in contrast to other experimental species including non-human primates and in humans is succinctly captured in an Adverse Outcome Pathway table (Table 1), taken from ECETOC 2013, which is based upon the best available interpretation of the existing data

III. Review of Epidemiology Studies: Contrasting the experience of laboratory rats with humans

A. ANSES CLH Report does not discuss Coal Miner Epidemiology Studies or any PSP Epidemiology Study

In the ANSES document on TiO2, the authors do not contrast the human epidemiological literature on “lung overload” with the rat study results to gain a perspective on human risk assessment. ANSES bases its proposed carcinogenicity classification of TiO2 on studies of laboratory rats only. In the section on “Carcinogenicity”, the CLH report states: “Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable….” ANSES should provide an objective discussion of the many peer-reviewed epidemiological studies on PSPs in the scientific literature.

We draw the Committee’s attention to ECHA’s recent “Draft Guidance on information requirements and Chemical Safety Assessment Appendix R7-1 Recommendations for nanomaterials”, where ECHA notes that a recent “epidemiological study evaluating the underlying cause of death for 9033 underground coal miners from 31 US mines after 37 years of follow-up (Graber et al., 2014), found a significant relationship between coal mine dust exposure and lung cancer mortality. Hence, the data obtained from rats may still be useful to predict the effects in humans.” While we welcome ECHA’s approach to include data on Epidemiology to inform their conclusion, it is surprising that ECHA does not review and consider other coal miners epidemiology data as well as the Graber et al., 2014 study. The Graber et al., (2014) study, which is “positive”, is the only study cited by ECHA, out of the vast number of predominantly negative coal miner studies that are available, to emphasize the possible relevance of effects seen in rats under “overload” conditions for human hazard and risk assessment. Appendix B of this document provides a discussion of the Graber et al., 2014 study, placing it in perspective of the entire coal miner epidemiological studies. We draw the Committee’s attention to the fact that the authors of this US study even acknowledged, in a reply to a Letter to the Editor, that there are qualitatively better epidemiological studies available than their US coal miner study.

In the following section, we provide a comprehensive discussion of coal miner epidemiology studies. The results of these studies indicate that PSPs, such as TiO2 do not increase cancer risk in humans.

B. Workers with potential lung overload: Coal Miners
Data on coal miners provide the best available human evidence with which to explore lung overload questions. Using eight studies conducted between 1956 and 1986 from a total of 1,225 miners in the US and UK, Mauderly (1994) converted the lung burden of coal dust into units of specific lung burden and showed that long-term coal miners commonly accumulated dust burdens in the range of 7 to 14 mg per g lung. This value indicates that the dust burdens in heavily exposed human lungs are in the same range as, or greater, than in the heavily exposed experimental animals seen in chronic bioassays. In spite of these high lung burdens, coal dust exposure has not been shown to significantly increase the risk of lung cancers among miners (IARC, 1996).

Coal miners do not suffer from elevated lung cancer risks (Stayner et al., 2011 and Morfeld, 2013). In an attempt to provide a perspective on risks of lung cancer under conditions of "lung overload", we reviewed mortality studies of coal worker and other dust-related industry cohorts. Exposure to coal mine dust particulate in miners has long been recognized as one distinct occupation with significant potential for exposure to dusts. It can be instructive to address the results of these studies in considering the potential human significance of high dose rat inhalation studies.

Intensive investigations in the US and in the UK showed that coal miners did not develop overload - even under high exposure conditions (Kuempel et al., 2001; Tran et al., 2014). Kuempel et al., 2001 studied pathologic data of 131 US coal miners (mean age at death: 67 years, average cumulative dust exposure: 107 mg-year/m3, 36 years of exposure, mean coal mine dust concentration: 3 mg/m3). The mean lung dust burden was 13.8 g (sd = 8 g) while the mean lymph dust burden, among the subset for which lymph data were available, was 1.6 g (sd = 1.6 g).

Tran and Buchanan analyzed the pathological data of 423 UK miners: mean age at death: 67 years, average cumulative dust exposure: 256 gh/m3 = 145 mg-year/m3 (assuming 220 working days per year with a shift length of 8 h) (Tran et al., 2014) The mean lung dust burden was 14.4 g (sd= 11.7 g) while the mean lymph dust burden, among the subset for which lymph data were available, was 2.3 g (sd= 1.0 g).

Kuempel et al., (2001) referred to a dosimetric model developed in 1997 and found that a three-compartment model with no clearance breakdown fit the lung burden best when analyzing the autopsy data of the US coal miners (Kuempel et al., 2001). Tran and Buchanan tested this hypothesis in their independent and larger set of 423 UK miners and produced the same result (Tran et al., 2014). A best fit was achieved when the alveolar clearance rate was set invariant, i.e., the two independent studies present convincing evidence that even under the historically-high dust exposure scenarios of coal miners, no lung overload occurred in humans (Kuempel et al., 2001 and Tran et al., 2014).This result and the related Gregoratto model (Gregoratto et al., 2010) were confirmed once more in a more recent study using both data sets in a Bayesian analysis via Markov Chain Monte Carlo simulations (Sweeney et al., 2013).

In the most recent study on US coal miners, the lung cancer standardized mortality ratio (SMR) was only slightly elevated (SMR=1.08, 95% CI: 1.00-1.18) (Graber et al., 2014). This excess is unexceptionable because of the higher proportion of smokers at the start of the study in 1969/1970 (current smokers: 54%, Supplement Table IV) in comparison to the US male population in 1970 (current smokers: 44.1%). Internal analyses showed an association of lung cancer mortality with coal mine dust exposure but only during the last follow-up interval from 2000 to 2007. All follow-up periods until 2000 showed no association between coal mine dust exposure and lung cancer (Graber et al., 2014 and Attfield, 2008). The study relies on smoking information collected only at the start of

follow-up. The models are unable to adjust for smoking habits after leaving work. Note that current smokers smoked less when working as a coal miner than current smokers in the US male population (prevalence of smoking more than 25 cigarettes per day: 12.4% among US coal miners vs. 28.0 % in the US male population). This difference is probably caused by prohibition of smoking when working underground. It is plausible that smoking coal miners have increased their intensity of smoking after cessation of work underground and that this may have caused an increase in lung cancer mortality during the last follow-up period when most coal miners of the cohort have already stopped working underground (See Miller et al., 2010). The US study has an incomplete assessment of jobs held; no start and end date of jobs/tasks held before 1969/1971; no information on jobs/tasks held after start of follow-up in 1979/1971 and no end date of working as a coal miner for 16% of cohort members (Graber et al., 2014). Thus, only a crude assessment of exposure to coal mine dust up to the start of follow-up was possible: no time-dependent exposure analysis or lagging or lugging of exposures could be done. Crystalline silica concentration data suffered from additional limitations because measurements were available only after 1982 but had to be allocated to the jobs held before 1969/1971. Shortcomings and errors of this study were discussed in two Letters to the Editor (Taeger et al., 2014 and Morfeld 2014). A detailed review of this study is noted in Appendix B)

The largest study to date with better assessment of exposures in a time-dependent manner was performed in the UK (Miller et al., 2010): the overall evidence does not support an excess in lung cancer risk among coal miners, when compared to the general population or in internal analyses of the effect of coal mine dust exposure (Graber et al., 2013). Similar results were found in Germany, based on a detailed and time-dependent exposure assessment in an analysis of lung cancer mortality and incidence data (Morfeld, 2013; Morfeld et al., 2002; Morfeld et al., 2004 and Morfeld et al., 2007).

We would like to emphasize that all coal miner mortality studies discussed in this section showed a link between coal mine dust exposure and coal worker's pneumoconiosis (CWP), a clear sign of substantial dust exposure and tissue reaction. Thus, even in the presence of pulmonary fibrosis, no increase in lung cancer was reported in relation to coal mine dust.

C. Workers exposed long-term to poorly soluble particles: Carbon Black Manufacturing

The mortality of CB production workers has been extensively studied in the USA and in Europe (Dell et al., 2015; Morfeld et al., 2006a ; Morfeld et al., 2006; Morfeld et al., 2007; Morfeld et al., 2009; Morfeld et al., 2010; Sorahan et al., 2001; Sorahan et al., 2007 and Wellman et al., 2006). Three major cohort epidemiological studies were performed in the UK, USA and Germany to investigate lung cancer mortality in CB production plants.

An update and extension of the retrospective mortality study of US carbon black workers evaluated a cohort of 6634 workers employed in the carbon black industry dating back to the 1930s (Dell et al., 2015). The mortality follow-up was extended until December 31, 2011 and a quantitative assessment of individual cumulative exposure to inhalable carbon black dust conducted. The results showed no increase in lung cancer or any other malignancy in either the total or inception cohorts: Lung cancer mortality was decreased in comparison to state-specific reference rates (184 observed deaths, SMR = 0.77; 0.95-CI: 0.67 to 0.89), and for all cancers (512 observed deaths, SMR=0.79, 0.95-CI: 0.72–0.86). Internal exposure-response analyses showed no convincing link between carbon black exposure and lung cancer mortality. In summary, the authors of the study concluded: "Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or non malignant respiratory disease."

This retrospective US mortality study of carbon black workers is the largest cohort yet published in the world's literature. It includes over 6000 workers employed in the carbon black producing industry dating back to the 1930s. Both an inception cohort, designed to reduce potential survivor bias, and a total cohort were individually evaluated for mortality risks. A notable advantage of this epidemiology study is the detailed individual cumulative exposure assessments that were analyzed with uniform job titles to enable robust dose response analyses. The availability of nearly 30 years of actual carbon black airborne monitoring data back to 1979 facilitated calculation of reliable exposure estimates.
The results showed no increase in lung cancer or any other malignancy in either the total or the inception cohort. The dose-response analysis showed no link between carbon black exposure and risk of malignancy. Another notable advantage of this study is the exceptional level of ascertainment achieved in identifying vital status, in that 98.5% of eligible cohort members were identified as alive or deceased.
In summary, the authors of the 2015 study concluded: "Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or non malignant respiratory disease."
The most recent comprehensive international evaluation of potential human cancer risks due to carbon black (CB) exposures was performed by an IARC working group in February 2006 (Baan et al., 2006). The working group identified lung cancer as the most important endpoint to consider and exposures at CB production sites as the most relevant for an evaluation. Three major cohort epidemiological studies were performed in the UK, USA and Germany to investigate lung cancer mortality in CB production plants. These studies, all of which preceded the USA mortality study described above, were critically reviewed by an IARC working group in 2005. This same working group of scientists also reviewed the literature on TiO2 regarding its potential to cause cancer.
A UK cohort study on 1,147 workers at five plants (Sorahan et al., 2001) found a standardised mortality ratio (SMR) of 1.73 (61 cases, 0.95-confidence interval (CI): 1.32, 2.22) but no trend across crudely assessed cumulative exposure, lagged up to 20 years. Elevated lung cancer SMRs were observed at two plants, the SMRs of the other three plants were unexceptionable. A German study on 1,528 workers at one plant (Wellmann et al., 2006, Morfeld et al., 2006a, Buechte et al., 2006, Morfeld et al., 2006b) estimated an SMR = 1.83 (50 cases, 0.95-CI: 1.34, 2.39) but could not find any positive trends with CB exposures. However, the German study identified smoking and prior exposures to known carcinogens as important risk factors that could explain the major part of the excess risk (Morfeld et al., 2006a). A US cohort study on 5,011 workers at 18 plants (Dell et al., 2006) calculated an SMR = 0.85 (127 cases, 0.95-CI: 0.71, 1.00) and found no trend across time since first exposure and duration of exposure in years.

The working group at IARC concluded that the evidence in humans for the carcinogenicity of CB was inadequate (Baan et al., 2006; IARC 2006).

Since the IARC 2006 evaluation, in an extended follow-up of the UK study, Sorahan and Harrington (2007) applied a novel exposure metric ("lugging") while hypothesizing that CB may act as a late stage lung carcinogen at plants with elevated SMRs. If so, the elevated SMRs of lung cancer should decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative CB exposure ("lugging" the exposure by 15 years means to count only exposures received during the last 15 years). Sorahan and Harrington (2007) observed both phenomena in those (and only those) two UK plant cohorts that had elevated lung cancer SMRs. The authors asked for repetitions of their surprising findings in independent settings. Morfeld and McCunney (2007) tested the hypothesis of Sorahan and Harrington (2007) in the German study. Neither a decreasing SMR after cessation of exposure was observed nor a positive relationship with "lugged" cumulative CB exposure although the German cohort showed a

clearly elevated lung cancer SMR. Therefore, Morfeld and McCunney (2007) were unable to lend support to the new hypothesis generated by Sorahan and Harrington (Morfeld and McCunney, 2007).

More recent studies have also been published (Morfeld and McCunney, (2009 and 2010). In a detailed analysis of the German CB cohort, additional analysis was conducted to address potential "lugging" effects. As noted above, "lugging" is a term introduced by Sorahan and Harrington (2007) to account for the most recent exposures with respect to health risk. Methods such as Bayesian analysis were employed to explore all potential risk factors and confounders that may have contributed to the results. These additional studies provide further support for the lack of a significant increased risk of cancer as a result of working in the CB industry.

The relationship between workplace exposure to CB and lung cancer risk was examined in two large population-based case-control studies carried out in Montreal, Canada (Parent et al., 1996; Ramanakumar et al., 2008). Interviews for Study I were conducted in 1979–1986 (857 cases, 533 population controls, 1,349 cancer controls) and interviews for Study II were conducted in 1996–2001 (1,236 cases and 1,512 controls). Detailed lifetime job histories were elicited and a team of hygienists and chemists evaluated the evidence of exposure to a host of occupational substances, including CB. Lung cancer risk was analyzed in relation to each exposure, adjusting for several potential confounders, including smoking. Subjects with reported occupational exposure to CB, TiO2, industrial talc and cosmetic talc did not experience any detectable excess risk of lung cancer.

Overall, as a result of these detailed investigations, no causative link of CB exposure and cancer risk in humans has been demonstrated. This view is consistent with the IARC evaluation in 2006. The newer US study (Dell et al., 2015) not available to the IARC 2006 working group, also supports the lack of an excess lung cancer risk among CB production workers.
D. Workers exposed to Toner and Titanium dioxide: No lung cancer excess risk in workers
Similar results have been observed with other particles, such as toner and TiO2. Carbon black is used in the production of toner. Some laser printers and photocopiers use toner, which commonly contains carbon black mixed with a heat sensitive polymer. These products are ubiquitous in businesses and homes all over the world. The purpose of the information below is to summarize studies of the toner industry in which carbon black exposure was measured, assessed, or discussed.
As with coal miners, no lung cancer excess risks were found in large cohorts of toner-exposed workers. A large retrospective study of mortality risks of 33,671 employees occupationally exposed to toner was conducted (Abraham et al., 2010). The exposed group included employees involved in the manufacturing of toner and customer service engineers who serviced copiers in the field. All-cause SMRs for toner-exposed populations were 0.65 and 0.84 for white men and women respectively. SMRs for all cancers including lung cancer were lower than 1.0. There was no evidence that toner exposure increased the risk of all-cause mortality or cause-spe¬cific mortality for the 23 categories of death analyzed. No evidence of adverse effects on lung function or chest films was noted; no evidence of excessive inflammatory, allergic, or oxidative stress reaction was present in the toner-handling workers as compared to the non-specifically exposed workers (1504 male workers in a Japanese toner and photocopier manufacturing company, means of personal 8h respirable dust concentrations spanned from 0.012 mg/m3 in toner manufacturing to 0.989 mg/m3 in toner and photocopier recycling) (Kitamura et al., 2014).

No lung cancer excess risk was found in studies of TiO2-exposed workers. A multi-center

occupational epidemiology study was performed in Europe that enrolled 15,017 workers long-term exposure to TiO2 (Boffetta et al., 2004). Four US production plants with a total of 4,241 exposed workers were studied (Fryzek et al., 2003).

The results of Kuempel et al., 2009 showed that the rat findings are difficult to rely on when the toxicological effects of PSP dust in humans are to be estimated in quantitative terms. Kuempel et al., 2009 commented on a comparison of rat-based risk estimates (MLE, maximum likelihood estimates) by translational toxicology and epidemiological risk assessments: "Regarding the magnitude of the excess risk estimates, the rat-based MLEs were clearly higher than the human-based estimate for coal dust (which was negative); however, the rat-based estimates (MLEs and 95% UCLs) did not exceed the 95% UCL from the human study. For carbon black, the rat-based excess risk estimates exceeded those from the human study, but the differences were not statistically significant. For titanium dioxide, the rat-based excess risk estimates (MLE and 95% UCL) were lower than the 95% UCL of the human studies, although the MLE from Fryzek et al., was negative" (Kuempel et al., 2009). For coal mine dust and carbon black these authors found that the rat estimates are in excess in comparison to the humans. Because of statistical imprecision, such a statement could not be derived for TiO2 but the authors stated that the epidemiological findings on TiO2 were negative.

In summary, no causative link between exposure to well-investigated respirable PSPs (including some nano-structured dusts), such as coal mine dust, TiO2, toner or CB, and an excess in lung cancer risk in humans has been demonstrated.
E. Summary: Weight of evidence assessment of epidemiology literature
Overall, well-conducted epidemiology studies of workers exposed to PSPs, including CB, coal and TiO2 do not indicate an increased risk of lung cancer. The rat inhalation studies in which female rats-but not male rats, mice, guinea pigs, hamsters or monkeys develop lung cancer are not valid for predicting lung cancer in humans. It is our considered view that the overwhelming evidence from well-conducted occupational epidemiological investigations on workers exposed to a range on PSPs, including carbon black, TiO2 and coal mine dust, are adequate, reliable and representative human data, and provide, "strong evidence that the mechanism of tumour formation in the female rat is not relevant for humans". Therefore, in a weight of evidence assessment taking into consideration, epidemiological findings, experimental interspecies differences, mode of action findings and accepting that lung tumours induced by PSPs such as TiO2, are unique to the rat and not predictive for humans, the classification for carcinogenesis (CAT 1B) proposed in the ANSES report is not defensible.

IV. Conclusions
The ANSES document does not provide reasonably convincing scientific evidence for the use of rat inhalation studies to classify PSPs (including TiO2) as presumed (CAT 1B) or even suspected (CAT 2) human carcinogens. The failure of the ANSES CLH report to directly assess the extensive human epidemiology literature of workers exposed to PSPs in conjunction with the rat results is a major scientific shortcoming and makes it unreliable for the purposes of human risk assessment and classification. In our opinion, a thorough examination of the entire relevant scientific database leads to the conclusion that for TiO2, no CLP classification for carcinogenicity is appropriate.

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VI. Appendix
A. Comments on the GBS document of the German MAK Commission
ANSES suggested a 1B carcinogenicity classification of TiO2 (carcinogenic to animals) based on the overload phenomenon in rats, also referring to the German MAK document

on GBS (granular biopersistent particles without known specific toxicology) which states that all GBS are carcinogenic to animals and humans, including titanium dioxide (Hartwig 2014).

Apparently, ANSES agrees completely with the description of MAK's GBS approach as given in Morfeld et al., (2015a) on page 2 and 3. They used virtually an identical wording in their conclusion on page 60, although the report did not refer to Morfeld et al., (2015a). It is an important omission that the critical review of Morfeld et al., 2015a was not cited and discussed by ANSES in their CLH report on TiO2. We add that ANSES presented no scientific discussion of the MAK approach. MAK's GBS document was simply cited by ANSES as evidence in favour of a cancer classification of TiO2.

The MAK Commission developed in their GBS document (Hartwig 2014) a new approach and translated findings from rat overload experiments quantitatively into HECs (human equivalent concentrations) to derive an OEL (occupational limit value) for GBS. Importantly, the MAK Commission also performed a cancer classification of GBS that depends on the reliability of the translational toxicology models applied. The MAK Commission stated: "… the data obtained in test animals on the potential carcinogenicity of particles can be applied to humans if species-specific conditions (anatomy and histology of the respiratory tract) are taken into account" (Hartwig 2014, p. 19) (see the MAK Committee's manifesto on the carcinogenicity classification in Hartwig 2014, p. 63.)

Morfeld et al., 2015a commented: "This new MAK approach is a substantial departure from principles that have been used for many years in including results of human studies, most notably epidemiological findings. To rely so heavily on translational toxicology models only, the new approach must be transparent, consistent, and evidence-based". In their review, the authors examined the scientific assumptions used by the MAK Commission.

Briefly, Morfeld et al., (2015a) emphasized that this classification depends on the reliability of the translational toxicology models. Moreover, goodness of models requires the correctness of input data. We adopt the comments by Prof. Hartwig (Hartwig 2015), chair of the MAK Commission, on Morfeld et al., (2015a) and the reply from the authors (Morfeld et al., 2015b) to Prof. Hartwig. Below we want to summarize and highlight the discussion about the correctness of models and input data with respect to the MAK's recommendation. It is a further and important omission that ANSES did not refer to this published exchange about the scientific validity of MAK's GBS approach.

Morfeld et al., 2015a concluded: "The calculations described in the MAK document (Hartwig 2014) on GBS are based on a number of incorrect assumptions and calculations related to the use of lung surface area, particle clearance rates and deposition fractions among others which are shortcomings that affect both translational overload models (Model A and Model B) used to derive the HEC for GBS. The methods applied do not reflect state of the art techniques and cannot be independently replicated since the hyper link cited by the MAK Commission no longer leads to the program version the Commission and Pauluhn (2011) applied (MPPD 2.0). In Pauluhn (2011), calculations were based on a Fortran program that is not publicly available. More importantly, the approaches are inconsistent as they rely on conflicting assumptions. The resulting errors are so large that the MAK Commission's suggestion (Hartwig 2014) as to how to translate inflammation/overload findings from rats to humans is unreliable and the OEL proposal is unsubstantiated. This also affects the justification of the MAK Commission's cancer classification which is related to humans (Carcinogen Category 4) but based on overload inhalation experiments with rats. This classification relied on the validity of the proposed translational overload models."

Thus, it is inappropriate to cite MAK's GBS approach in ANSES report as evidence for a cancer classification of TiO2 without considering the detailed review by Morfeld et al., 2015a and the letter exchange published (Hartwig 2015, Morfeld 2015b). The GBS approach should be discussed by ANSES in detail and evaluated on the background of the raised criticisms or the passage about GBS should be dropped.

In the following, we like to highlight just a few aspects of MAK's translational toxicology models that should be important in any scientific evaluation of the MAK's GBS approach. We do not repeat the more general problems related to e.g., the AOP (adverse outcome pathway) analysis and particle surface area metric and refer to Morfeld 2015a, Morfeld 2015b for any details.

Proper input data and consistent mathematical structures are critical for goodness of models

1) To derive an exposure limit (MAK value), the MAK commission applied two different models. One approach based on retained particle mass per alveolar surface area (Model A) and another on retained particle volume per macrophage pool volume (Model B).

Model A: wrong density correction

The MAK Commission considered that in Model A "the particle clearance and the retained particle dose is not dependent on the particle density per se but on the particle volume (Density = mass/volume)." Interestingly, the MAK commission applied alveolar clearance rates invariant of "density" and "volume" (given the same species), and used the identical clearance rates for substances with very different densities in Model A. This application by the MAK Commission is contradictory to Model A as published and consequently the derivate is unreliable.

Model B: wrong rule of three
Model B used by MAK is based on the second derivations of Pauluhn (2011). However, the units were confused and the standardization by rat lung mass or rat body weight is varying and inconsistent (Morfeld et al., 2015). Hartwig (2015) did not address this important error in their reply (wrong application of the rule of three).

2) Outdated and not available
The MAK Commission employed the MMPD model Version 2.0 to calculate the particle dose deposited in the lung. In fact, this program version is outdated and not available under the hyperlinks provided by the MAK Commission. Hence, the calculation is not reproducible.

3) Even not reproducible with outdated program
The MAK commission supposedly asked two experts to cross check with Version 2.0, the correctness of the deposition fraction used in Model A. Whereas Morfeld et al., 2015 criticized that the deposition fraction as used in Model B – not Model A - was unjustified. Morfeld et al., 2015 showed that the deposition fraction used in Model B cannot be reproduced applying the input data published in Hartwig 2014, neither with the current nor with the outdated MPPD program version.

4) Alveolar lung surface area
The MAK Commission used 57.22 m2 for the human alveolar surface area. This should represent a normal exhalation value. However, the background of this value could not be substantiated. Instead, data from Gehr et al., (1978) should have been used which are

referred to as the current gold standard. These authors reported a surface area of 144 m2 at maximum inhalation. Furthermore, we have to note that the main discussion does not deal with the absolute value of the lung surface area but the ratio of lung surface areas between humans and rats. Because the lung surface area ratio is used in Model A to translate findings from experimental rats to workers, we have to consider both, rat and human surface area data. To be noted, the methods used to determine the surface areas both for humans and for rats should be same, in order to derive a reliable ratio. Furthermore, an unbiased estimate of the human/rat ratio based on state-of-art methods is 349, but not 193 as applied in (Hartwig, 2014).

5) Average clearance half-time
An average clearance half-time of 400 days was applied for humans by the MAK Commission in Models A and B, which corresponds to the clearance half time from the alveolar to bronchial region according to Gregoratto (2012), a state-of-the-art paper. In contrast, a half time of about 255 days is expected from the alveolar compartment considering both, the clearance into the bronchial region and into the interstitium, again according to Gregoratto (2012). We have to consider that MAK's Model A and B limit all adverse effects to an interaction of deposited dust with structures/cells within the alveolar compartment. Thus, 255 days should be used in calculations based on Models A and B, instead of 400 days.

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B. Comments on the "Respiratory disease mortality among US coal miners; results after 37 years of follow-up" by Graber et al., 2014

The ECHA draft guidance on information requirements and Chemical Safety Assessment Appendix R7-1 Recommendations for nanomaterials" mentioned a coal miner study, not discussed in the ANSES report. On page 10, they say that the overload has relevance for humans because of a new coal miner study from the US (Graber et al., 2014). To be more precise, ECHA reported on the general overload discussion by Valberg et al., 2009 (P. Valberg, J. Bruch, RJ McCunney "Are rat results from intratracheal instillation of 19 granular dusts a reliable basis for predicting cancer risk?"," Regulatory Toxicology and Pharmacology, vol. 54, no. 1, p. 72–83, 2009) and commented on page 10 on Valberg et al., 2009 as follows:

"They argued that the response of rats to PSP lung overload is stereotyped and unique to that species and pointed towards human exposure to justify this. Specifically, they noted that workers historically exposed to potentially lung-overloading burdens of inhaled dust (e.g., coal workers, underground miners using diesel equipment) do not exhibit an established lung-cancer excess despite the potential for lung overload. However, a recent epidemiological study evaluating the underlying cause of death for 9033 underground coal miners from 31 US mines after 37 years of follow-up (Graber et al., 2014), found a significant relationship between coal mine dust exposure and lung cancer mortality. Hence, the data obtained from rats may still be useful to predict the effects in humans."

Thus, a critical discussion of Graber et al., 2014 is necessary.

Background on Graber et al., 2014

The Graber et al., (2014) is an updated US coal miner mortality study with an extended follow-up for 37 years. The study used cumulative coal mine dust exposure to examine exposure-response associations. Negative findings were reported in coal miners with respect to lung cancer from earlier studies. In contrast, the study of Graber et al., (2014) found "an overall excess of lung cancer mortality (SMR = 1.08; 95% CI 1.00 to 1.18) and a significant association with cumulative coal mine dust exposure and lung cancer in the last decade of follow-up 2000-2007". The limitations of the exposure assessment and analysis methods are noted in their discussion.

We reviewed the Graber et al., (2014) report, in particular the association between coal mine dust and lung cancer mortality, and we like to offer our view on it. We adopted the viewpoints in two Letters to the Editor (Morfeld 2014; Taeger et al., 2014).

Included below are our comments on the exposure assessment and analysis methodology, as well as overall findings and conclusion.

Comments on the exposure assessment

The study suffers from an incomplete assessment of occupational histories in coal mine workers. There was no information on jobs held after 1969/1971, and no end date of working as a coal miner for 16.2% of cohort members. In addition, translation of limited environmental measurement values into individual exposure data is another source of inaccuracy.

(1) Cumulative coal mine dust exposure was defined as the sum of the products of each job-specific dust concentration and the duration of time worked at that job. Some exposure assessments were based on some measurements collected during environmental surveys at certain US mines by the Bureau of Mines between 1968 and 1969. In addition, the exact duration of specific jobs held could not be derived from the incomplete job histories. To overcome this sparse data situation in this study, the strong assumption was made that the jobs of the miners and the level of exposure have not changed after study enrolment.
Hence, only a crude assessment of exposure to coal mine dust up to the start of follow-up was possible. Consequently, the risk estimates based on the mean cumulative coal mine dust exposure are questionable.
Crystalline silica concentration data suffered from additional limitations because measurements were available only after 1981 but had to be allocated to jobs held before 1969/1971. This may have lead a potential upward bias of risk estimates assuming that exposure to quartz decreased with time.

(2) Due to the lack of entry and end dates of jobs, potentially different employment patterns could not be considered and the exposure could not be handled in a time-dependent manner. Thus, the results suffer from the limitation due to the Healthy Worker Survivor Effect (models that adjust for time since last employment do not solve this problem).

(3) For the reason of lacking of end dates of employment, lagging or lugging time analysis was not possible in this study.

(4) Sensitivity analysis examined the sub-cohort members with known end date working as a coal miner. The mean cumulative coal mine dust and respirable silica dust exposure estimates were 83.0 mg/m3-year (SD =41.3) and 4.1 mg/m3-years (SD=1.8), while the mean values of the whole cohort were 64.6 (SD = 46.4), and 2.6 (SD = 1.0), respectively. However, the authors argued that "the coefficients for the exposure-response relationships with each of the outcomes were statistically similar for the extended compared with the original estimates". Obviously, the distribution of the cumulative exposure values differs between the sub-cohort and the whole cohort.

Comments on Analysis Methodology

The authors performed external and internal analyses, which both contain errors.

(1) As a result from external analysis, the overall lung cancer SMR was slightly elevated (SMR=1.08, 95% CI: 1.00 -1.18), disregarding the fact that a higher proportion of smokers (current smoker: 54%) at the start of follow-up in 1969/1971 than that of the US male population in 1970 (44.1%) [Morfeld 2014]. The authors used age-, calendar-, sex-, and race-specific mortality ratios, without adjusting for smoking status. Axelson's approach is, however, available to adjust for the confounding effect of smoking.

Referring to the approach of Axelson (1978), we calculated the correction factor considering the compositions of non-smokers (25%), former smokers (30%), and current smokers (45%) in the reference population of US male in 1970, and compositions of non-smokers (20.4%), former smokers (25.6%), and current smokers (54.0%) of the study population. The correction factor might lie between 1.2 and 1.6. Even a 10% correction would reduce the tentative SMR below unity.

(2) Taeger et al., pointed out in their Letter to the editor that SMRs differed considerably

between regions, in particular for lung cancer. They suggested to use regional rates for SMR calculation, and combined the results finally. The authors acknowledged that the suggested method would be more reasonable.

(3) The authors emphasised that the results from the internal comparison should be focused on. In Table 4 of Graber et al., the HRs of cumulative coal mine dust and respirable silica per mg/m3-year were falsely calculated. A B-coefficient of 0.1271 would yield a HR of 1.136, and B-coefficient = 0.0191 yields HR = 1.02, as pointed out by Taeger et al., in their letter as well. Hence, both results in this respect are obviously erroneous, which has NOT been considered in their Erratum, which was published in October 2014.

(4) In addition, Table 4 demonstrated apparently that smoking, either in qualitative or in quantitative assessment, was associated with an increased risk of lung cancer. Therefore, the conclusion of the authors that "Our findings support …… from malignant and non-malignant respiratory diseases even in the absence of smoking" is not in line with the results presented. The conclusion should be restricted to mortality from COPD.

(5) Table 5: a significant association between cumulative exposure to coal mine dust and lung cancer was shown only for the time period 2000 – 2007. There was substantial difference of risk estimates, both in magnitudes and direction, across the time periods. Therefore, it is of interest to see the distribution of the cumulative exposure according to time period. Furthermore, the definition of time periods with differing length (20, 10, and 8 years) seemed to be arbitrary.

Additional errors are in the Abstract regarding the published confidence limits as pointed out by Taeger et al., (2014). The authors acknowledged "some transcription errors" und revised them in Erratum.

Comments on the overall findings and conclusions

(1) The most recent coal miner study in US (Graber et al., 2014) observed slightly excess mortality for lung cancer (SMR = 1.08; 95% CI: 1.00 – 1.18), comparing with the general population. SMR as risk measure has its limitation due to the comparability with the reference population, here in particular with respect to smoking status. Despite the higher prevalence of active smokers in the study population, the authors did not adjust for the confounding effect of smoking. Axelson's approach can be applied to adjust for different composition of smoker and non-smokers in the study population. The tentative SMR would reduce substantially below unity.

(2) The authors emphasize that the major findings of the study are based predominantly on internal comparison. The quantitative exposure-response analysis showed significant association between coal mine dust exposure and lung cancer. The HRs from the Cox regression models are, however, obviously erroneous. Nevertheless, the results are not revised in their Erratum.

(3) The study has some severe inherent shortcomings. Firstly, only a crude exposure assessment was possible, i.e., translations from hygiene measurements to individual exposure is inaccurate. Secondly, the job duration of a specific job activity was not known for many miners. Consequently, the cumulative exposure measure must be inaccurate and the risk estimate for cumulative exposure per unit is potentially biased.

(4) All follow-up periods from 1970 to 1999 showed no association between coal mine dust exposure and lung cancer, except that of 2000 to 2007. This might raise the

question if coal mine dust may act as a late stage lung carcinogen. In an extended follow-up of the UK study of Carbon Black (CB), Sorahan and Harrington (2007) applied a novel exposure metric ("lugging") to study if the elevated SMRs of decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative exposure.
Nevertheless, the study of Graber et al., (2014) does not provide the adequate information to address this issue analytically.

The study relies on smoking information collected only at the start of follow-up. The models are unable to adjust for smoking habits after leaving work. Note that current smokers smoked less when working as a coal miner than current smokers in the US male population (prevalence of smoking more than 25 cigarettes per day: 12.4% among US coal miners vs. 28.0 % in the US male population). This difference is probably caused by prohibition of smoking when working underground. It is plausible that smoking coal miners have increased their intensity of smoking after cessation of work underground and that this may have caused an increase in lung cancer mortality during the last follow-up period when most coal miners of the cohort have already stopped working underground [see the discussion of this issue in Miller and MacCalman 2010].

The authors stated in their reply to a Letter to the Editor (Morfeld 2014): "We agree with Dr. Morfeld, and stated in our article, that the British study of coal miners (Miller and MacCalman 2010) had better exposure data than our study". It is important to note that the British study did not find association between coal mining and lung cancer risk, neither when compared to the general population or in internal analyses of the effect of coal mine dust exposure (Miller and MacCalman 2010). The same is true for all other analyses published on the US study (Attfield and Kuempel 2008). Similar results were found in Germany, based on a detailed and time-dependent exposure assessment in an analysis of lung cancer mortality and incidence data (Morfeld et al., 2002, Morfeld et al., 2004, Morfeld et al., 2007).

It is not a reliable "weight of evidence approach" to base all conclusions about coal miners cancer risk on the study of Graber et al., 2015 alone while ignoring the better UK study and the evidence from other countries. In addition, the important limitations of Graber et al., (2015) should be addressed as outlined in two Letters to the Editor (Morfeld 2014, Taeger et al., 2014) and a recent review (Morfeld et al., 2015).

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ECHA note – A non confidential attachment was submitted with the comment above. ANSES Proposed Classification of TiO2 - Comments by CB4REACH - 14 July 2016 - FINAL.pdf

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	United Kingdom	Toy Industries of Europe	BehalfOfAnOrganisation	320
Comment received				
The proposed classification of Carc 1B is considered to be not appropriate for the following reasons. In terms of general data quality, the animal studies on which the proposal is based are in general graded under Klimisch rules as class 3 (or unreliable). Only one				

rodent study that is used to support the proposal is graded higher and this is graded as class 2 or reliable with restrictions. It is therefore not considered reasonable to base a classification that will have a significant negative socio-economic impact on such data. More fundamentally, the suggested mode of action of carcinogenicity as a genotoxic process related to the generation of reactive oxygen species secondary to an inflammatory response is not specific to titanium dioxide; but can be considered to be a generic mode of action linked to lung tissue exposure to a range of biologically persistent granular material. Importantly, there is no evidence presented that specifically addresses the intrinsic toxicity of the titanium ion. In the majority of the studies that show evidence of inhalation carcinogenicity, there is a relationship with particle diameter with 15 to 40nm being the most likely be associated with an adverse effect. This is consistent with the study by Auffan et al (2009) that concluded that a particle diameter of less than 30nm was an indicator of potential carcinogenicity. This would also be consistent with a general hypothesis cellular uptake as a potential initiating event. The evidence is also weak for extrapolation to other species. Studies have shown that lung tumours as a result of TiO2 exposure in the laboratory are also likely to be rat specific as chronic exposures of mice and hamsters to submicron or nano sized TiO2 showed distinct species differences. The extrapolation to humans of the carcinogenic potential of exposure to TiO2 should therefore not be assumed without a rigorous appraisal of the human relevance. The classification proposal does not include a qualitative or quantitative comparison of the key events in the test animals and humans, and therefore does not adequately demonstrate sufficient human relevance. The lack of evidence from a number of epidemiological studies, even taking into account study limitations, for a strong suggestion of causality using the Bradford Hill criteria also casts doubt on the human relevance of TiO2 toxicity. From an exposure perspective, if it is accepted that biopersistent nano-sized particles may be related to carcinogenicity, then it must also be considered that the majority of TiO2 used in consumer products is pigment grade and consists of particles with a diameter exceeding 100nm. Alveolar clearance increases with particle size, therefore reducing exposure. Larger particles with a lower specific surface area are less reactive and by definition have a lower intrinsic hazard. A classification of Carc 1B that applies to the substance irrespective of particle size when the substance is intrinsically inert has significant consequences for the manufacturers of consumer goods when in the majority of cases exposure is extremely unlikely. The risk from the presence of titanium dioxide in liquid and solid matrices, particularly where the particle diameter is in any case >100nm is negligible. A classification of Carc 1B without qualification would affect many industries without a consequential decrease in the risks to human health. If is accepted that particles of titanium dioxide below a certain diameter may have an association with human carcinogenic potential through the inhalation route, then the harmonised classification should be published with a note that clearly explains that the classification only applies in these limited circumstances, and with a specific concentration limit that reflects the overloading exposure that has been shown to be the key event in initiating carcinogenesis in rodents.
Dossier Submitter's Response
See points 1, 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Finland		MemberState	321
Comment received				
Oral route The FI CA agrees with the conclusions that the fine-sized TiO2 is not a carcinogenic				

substance via oral route as it has been used as a food additive (E171) for decades and no ADI has been set (The EFSA Journal, 2004). However, data on nano-sized TiO2 is insufficient and no firm conclusion can be drawn about its carcinogenicity via oral route.

Dermal route
The FI CA agrees with the DS that TiO2 particles fail to penetrate to the intact skin, as it is shown in the literature independently of the particle size. Therefore, we support the conclusion that TiO2 does not meet the classification criteria for carcinogenicity via dermal route.

Inhalation route
The FI CA disagrees that the criteria for classification as Carc 1B; H350i is fulfilled. The data presented does not demonstrate sufficiently that all TiO2 particles are carcinogenic via inhalation. Deficiencies in the inhalation studies (extremely high doses, no characterization data of the aerosols and lack of the benchmark materials) raise up the uncertainty factor and weakens the strength of evidence for carcinogenicity of TiO2 via inhalation. The doses showing bronchoalveolar adenomas are extremely high (0.25 mg/l in a 2-year study [Lee, 1985]) and squamous cell carcinomas (SCCs) also reported with the high dose have been recognized as rat-specific non-neoplastic keratin cysts. The mode of action behind the adenoma and SCC development is most likely particle overload commonly associated with the exposure to poorly soluble particles (PSPs). This mode of action has been described by ECETOC report (2013) where the molecular initiating event in rats is described as impairment of clearance of particles in lungs (may result in neutrophilic inflammation, oxidative stress, secondary genotoxicity, DNA repair and apoptosis, and cell proliferation; Thompson et al. 2016). The relevance of this phenomenon for humans is uncertain but rats are known to be more sensitive to the effects of PSPs compared to other species (ECETOC, 2013; ILSI, 2000). To support this, TiO2 has not shown clear evidence of increased lung cancer among workers (IARC, 2010; NIOSH, 2011; CLH report [Proposal for Harmonised Classification and Labelling of TiO2] 2016). Since the weight of evidence for carcinogenicity of the studied TiO2 particles is insufficient these particles cannot be allocated to carcinogen category 1B. However, the sufficiency of data for the classification of TiO2 particles to carcinogen category 2 should be discussed separately, potentially by grouping different forms of TiO2 based on their characteristics (e.g. particle size) if justified, and clearly describing the characteristics of specific particles under discussion. Each form/group of TiO2 should then be evaluated separately to determine the need for CLH proposal(s).

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Thompson et al. 2016: Development of linear and threshold no significant risk levels for inhalation exposure to titanium dioxide using systematic review and mode of action considerations. Regulatory Toxicology and Pharmacology, epublished ahead of print.

Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Italy	Huber Italia SpA	BehalfOfAnOrganisation	322
Comment received				
We have been using this substance since 1970 and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any other materials in powder form, our workers use appropriate safety equipment to protect themselves from dusty materials. Additionally there is efficient ventilation and extraction installed in the related production areas for reducing the risk of having powder in the air. Moreover, as soon as Titanium Dioxide has been incorporated in the printing ink, and even more when e.g. a printed packaging is made from this ink, the TiO2 is no more available to be inhaled. But although the classification proposal is for TiO2 as inhalable dust, it would also affect liquid or pasty products and even readymade packaging. This is the consequence of a hazard- and not a risk-based legislation. ECHA note – A non confidential attachment was submitted with the comment above. Statement-HuberItalia-TitaniumDioxide.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	P.A. Jansen GmbH u. Co., KG	BehalfOfAnOrganisation	323
Comment received				
We have been using this substance for about 100 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				

Dossier Submitter's Response
See points 1, 2 and 4 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	ECKART GmbH	BehalfOfAnOrganisation	324
Comment received				
The proposed classification as Carc. 1b, H3501i (May cause cancer by inhalation) of titanium dioxide is based primarily on studies in rats in a "lung overload" context (p. 8, CLH report). In practice, this means that the rats were exposed to extremely high concentrations of titanium dioxide dusts, causing an impairment of normal pulmonary clearance. The "lung overload" phenomenon was only observed in studies with rats and mice. It should be mentioned in this context that the validity of "lung overload" studies is still part of the scientific discussion (please see guidance document to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Ver 4.1 June 2015). Other guidance documents (e. g. OECD Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453 or ECETOC Technical Report 122 "Poorly Soluble Particles / Lung Overload") also observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	United Kingdom		Individual	325
Comment received				
Human data does not suggest an association between occupational exposure to TiO2 and risk for cancer. (CLH report page 8) The exposure levels required are not clear and as far as reported no real life incidents in workers have been established as facts. In this case with such overwhelming evidence of safe use the classification is clearly not sound and should not be applied. In a product with such overwhelming evidence of safe use even in prolonged direct skin contact and inhalation during removal phases of paint and other coating plastics there can be no justification for such a risk classification. This appears to be confirmed by the findings on pages 20 through 23 of the CLH report and again on p39 "Cohort analysis suggested that the risks of developing lung cancer and other fatal respiratory diseases were not higher for TiO2-exposed employees than for the referent groups. Nested case-control analysis found no statistically significant associations between TiO2 exposure and risk of lung cancer, chronic respiratory disease and chest roentgenogram (X-ray) abnormalities." and on p 50 the conclusion is actually much clearer than the report suggests when it says "...no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data" and hence the groups findings on p66 are at best speculative and at worst erroneous, drawing too				

much from statistically insignificant findings when compared with real life available data. Based on the above there can be no justification whatsoever for classifying titanium dioxide as a potential carcinogen. Real life data in fact shows the opposite as reported in the CLH report and it is surprising to see such conclusions drawn.

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Japan	Kao Corporation	BehalfOfAnOrganisation	326

Comment received

We believe TiO2 does not have carcinogenic potential on humans from following reasons.

Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ.
The causal relation of the carcinogenicity associated with titanium dioxide has not been reported since titanium dioxide has placed in the market for more than 90 years.
In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.

According to two inhalation studies in rat, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumors, and adenocarcinoma were observed only in female rats, whilst it was not recognized that the increase of carcinogenesis or the increase of mortality in other two studies in rats or a study in mice. In addition, two inhalation studies in rat mentioned above, the study exposed rats to titanium dioxide at concentrations of 0, 10, 50, 250 mg/m3 showed that the maximum dosage caused bronchioalveolar adenoma, and it suggested overloading context (Lee, 1985 R2). It's known that mortality responses to inhaled particles of TiO2 differ by species, we consider that it's inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans.

We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses.

We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.

Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM. Please note that data were considered sufficient for the classification proposal for carcinogenicity.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany	CD-Color GmbHCo. KG	BehalfOfAnOrganisation	327
Comment received				
We have been using this substance for 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	France	Geholit chimie de peinture et de revêtements	BehalfOfAnOrganisation	328
Comment received				
We have been using this substance for as long as our company exists, wich is more than 35 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powders at all our workers are protected by local exhaust ventilation or by wearing appropriate dust masks. All controls of the strict french occupational exposure limits in the past years schow the reliability and effectiveness of these risk mitigation measures. During production all powders are well mixed into and entirely wrapped by binders. After incorporation in our products TiO2 is bound and no longer inhalable. Therefore no specific risks evolve from TiO2 and its specific chemical or physical properties for the users of our products. According to REACH a classification as carcinogen would oblige indutry to substitude TiO2 with materials not yet identified, not as well examined, or already banned by indutry due to negative properties. There is to date no known alternative in regard to low toxicity or high functionality of TiO2.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany		Individual	329
Comment received				
We have been using TiO2 for over 50 years and we are not Aware of any relatives between the use of TiO2 and the development of cancer by our workers. We use TiO2 in our coatings because it provides properties to the Quality of our products such as whiteness, opacity, brightness and stability. A very important aspect for us is, that TiO2 is classified as a harmless substance and has e.g. an approval for Food and medical products. There is no alternative that offers the same characteristics and harmlessness.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		Individual	330
Comment received				
1B is definetly not justified and supported for the pigmentary form 1B is also questionable for the nano-form (see the comment by the MAK commission in my submission) ECHA note – A non confidential attachment was submitted with the comment above. ECHA_ CLP_Comment.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Karl Wörwag Lack- und Farbenfabrik GmbH & Co. KG	BehalfOfAnOrganisation	331
Comment received				
Considering the proposed harmonised classification and labelling of titanium dioxide we are very concerned because we do not see any scientific and/or epidemiologic evidence that this substance should be classified as carcinogen category 1B (inhalation). This is substantiated by the fact that the available data on carcinogenicity from two experimental studies in rats published in the CLH report are not reliable sources for the purpose of classification of titanium dioxide as carcinogenic. From a toxicological point of view, these studies show several methodological deficiencies, including the study design, routes of application and the selection of concentrations for exposure of the test animals. Especially, the use of very high concentrations of titanium dioxide for inhalation exposure and the corresponding "lung overload" effects are not considered to be of toxicological relevance with respect to human health risk assessment. As stated in the OECD Guidance Document on Acute Inhalation Toxicity Testing (No. 39) "[…] Insoluble materials deposited in the alveolar region of the lung may accumulate over time with resultant impairment of particle clearance and particle-mediated inflammatory				

response. Hence, the lung dose accumulated over time may be decisive for the outcome of the test. […]". With respect to titanium dioxide, which is a very poorly soluble substances, not its intrinsic toxicological properties are crucial for acting as a carcinogen, but rather physiological processes leading to lung deposition and subsequent tissue inflammation caused by excessive exposure to its particles. Such mechanism are not substance-specific but rather characteristic for a wide range of dusts (e.g. coal dust, hardwood dust).
Thus, classification of titanium dioxide as carcinogenic is not adequate considering its intrinsic properties and would therefore lead to a misclassification. If a majority of the material we use would be classified as carcinogenic based on titanium dioxide, it would not assist our employees in being sensitive to the real toxicological risk from other substances having the same classification. In worst case, we would achieve a general ignorance when handling substances that bear a real risk for human health.

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	Cosmetics Europe	BehalfOfAnOrganisation	332

Comment received

As per the CLP criteria (2008R1272 — EN — 01.01.2016 — 006.001 — 153) for carcinogenicity classification, "The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (…). Such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen) or animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity".
In cases where the available evidence "is not sufficiently convincing to place the substance in Category 1A or 1B" a classification in those categories is not warranted;
"Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies "(…) "Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data."
In addition the Guidance on the Application of the CLP Criteria (2015) specifies that:
(P370) "substance are classified according to their potential to cause cancer in humans;
(P372) "Classification of a substance as a carcinogen requires expert judgment and consideration of many different factors (weight and strength of evidence) included in the hazard information on carcinogenicity".
In the case of titanium dioxide, some modes of action of tumour formation are considered to be not relevant to humans as demonstrated below. Where such a mechanism is identified then classification may not be appropriate", (Guidance on the Application of the CLP Criteria, June 2015, p 380/644).

1. Human Data on Carcinogenicity
In many large epidemiological studies on workers, no increased lung cancer risk in humans has been identified for Titanium Dioxide. (Fryzek et al, 2003; Boffetta et al, 2004). Thus, there is no evidence indicating a "causal relationship" between exposure to TiO2 and development of lung cancer in humans.

2. Animal Data on Carcinogenicity (Inhalation route)

Animal Data suggest that lung tumours associated exposure to Titanium Dioxide are only observed at inhalation doses high enough to overwhelm lung clearance mechanisms resulting in particle deposition, lung overload and subsequent toxicity leading to tumour formation; these conditions are not relevant for normal exposure conditions. At inhalation doses that do not overwhelm normal pulmonary clearance mechanisms (as recommended for selections of maximum dose in OECD guidelines 451/116), no evidence for increased lung cancer risk is identified for several animal models, including rats, mice and hamsters.
The classification proposal for TiO2 as Carc. Cat 1B – H350i requested by the French agency ANSES is based on evidence from two chronic inhalation studies (Lee et al., 1985; Heinrich et al., 1995) and two intra-tracheal instillation studies (Pott and Roller, 2005; Xu et al., 2010) performed in animals.
In an inhalation toxicity study (Lee et al., 1985), groups of male and female rats were exposed by whole body inhalation to TiO2 at concentrations of 10, 50, or 250 mg/m3 (1.5–1.7 µm mass median aerodynamic diameter MMAD) for 6 hours/day, 5 days/week, for up to two years. No increase in lung tumours was observed at 10 and 50 mg/m3 as compared to the control group. Lesions were observed at the highest concentration of 250 mg/m3 and re-evaluated by Warheit and Frame (2006). Benign keratinizing cystic squamous-cell tumours were found in both sexes. Only 1 out of 77 male rats and 11 out of 74 females showed such non-neoplastic lesions. Squamous metaplasia was observed in 2 females and poorly keratinizing squamous cell carcinomas were observed in 1 female. No other lesions were observed in males. The study was evaluated by NIOSH (2011) which pointed out that exposure concentrations greater than 100 mg/m3 cannot be considered as acceptable under current practice in inhalation toxicology studies. At 250mg/m3 the MTD (Maximum tolerated dose) is largely exceeded. Indeed, the results obtained at such high concentrations are not relevant given that they are observed only at concentrations far higher than those associated with any potential human exposure situation. Consequently, in a weight-of-evidence approach, the NIOSH questioned the relevance of the results obtained at 250 mg/m3 for classifying TiO2 as a carcinogenic to workers.
In the Heinrich et al. (1995) study, TiO2 was used as a negative control in 2-year chronic inhalation studies of diesel exhaust. Female Wistar rats and female NMRI mice were exposed to TiO2 (15–40 nm primary particle size) at an average concentration of approximately 10 mg/m3, 18 hours/day, 5 days/week. Mice and rats were exposed for up to 13.5 months and 24 months, respectively. In mice, the lung tumour rate in the TiO2 exposed group was lower than in the control group exposed to clean air. However, rats had developed lung tumours at the end of exposure. These tumours were not resorbed 6 months after the end of exposure since a statistically significant increase in adenocarcinomas was still observed. It should be noted however, that the study conditions did not follow the corresponding study guidelines (OECD 451). The major limitation of the study is that it has been performed in females only. Other limitations include changes exposure doses throughout the study, the selection of 1 exposed group only, the length of the daily exposure (18 h per day vs 6 h /day), the limited number of animals examined after standard 2 year lifespan (9 - rats), the extension of the observation period beyond 2 years (30 - rats), the lack of purity information for the nano scale TiO2. .
Similar tumours were observed following intratracheal instillation of TiO2 to female rats (Pott and Roller, 2005; Xu et al., 2010). Even if this method has often been used to assess inhalation toxicity, intratracheal instillation is not the physiological route of exposure to airborne particulates. In fact, intratracheal instillation bypasses the upper respiratory tract and its defence mechanisms, produces highly uneven patterns of lung retention (lung overload) and delivers an abrupt, concentrated (bolus) dose into the lung in a short period of time. These unusual exposure durations may overwhelm and overload specific respiratory defence mechanism and cause more severe lesions than usual

inhalation exposures (ECETOC, 2013). Indeed it has been shown that instillation of TiO2 caused more severe and early effects than inhalation due to the bolus dose (Driscoll et al., 1990). Thus, this exposure method is not relevant for human exposure situations and the results obtained in studies performed by intra-tracheal instillation should not be used to support a Carc. 1B classification proposal.

Taking into account the limitations of the studies (non-physiological route of administration, non-relevant high dose, animals of a single sex tested), the results obtained strongly suggest a species- specific sensitivity. Even if the CLH report mentions that a sex-specificity is not expected (p67), the above experimental evidence indicates that female rats bear more sensitivity to tumour formation following inhalation exposure to TiO2 under overload exposure conditions. Where such a mechanism is identified then classification may not be appropriate", (Guidance on the Application of the CLP Criteria, June 2015, p 380/644). It should be highlighted that under non-overload exposure conditions (5 mg/m3) in another chronic (24 months) study in female and male rats, no treatment-related carcinogenic effects following inhalation of TiO2 were observed (Muhle et al., 1989).

3. Relevance to Humans
Lung overload is a response observed only in rats, which are well-known to be very sensitive to these effects. Lung tumours were indeed observed in inhalation carcinogenicity studies in rats only, whereas similar findings were not observed in similar inhalation studies performed in mice, hamsters, rabbits, pigs and even primates.
Various scientific bodies have concluded that the rat lung tumours are not relevant to humans under relevant human exposure levels. An ILSI workshop (2000), which evaluated the relevance of the rat responses to particle overload for human risk assessment, concluded that under conditions of non-overload exposures, no carcinogenic potential is identified. Experimentally-induced lung tumours in rats occur in the alveolar and small airway regions of the lungs, unlike human lung cancers that tend to occur in epithelial cells at the bifurcations of the major airways (bronchi). These anatomical differences in site of origin of tumours add further uncertainty to the extrapolation of results obtained in rat studies to humans. We refer to the TDMA submission for a further detailed review on tumour types observed in rats and their relevance to humans.
As stated above, these considerations are consistent with the outcome of epidemiological studies on a potential association between the incidence of lung cancer in workers and their exposure to TiO2. None of the studies mentioned in the CLH report and reviewed by the IARC (2010) and the NIOSH (2011) provided consistent evidence of such an association. A recent review confirmed that epidemiological studies thus far have not been able to detect an association between occupational exposures to PSP and an increased risk of lung cancer (ECETOC, 2013).

4. Conclusion Toxicological / Scientific comments on the CLH proposal and dossier
In summary, there is no evidence of increased prevalence of lung cancer risk in Humans associated with exposure to TiO2. This is well acknowledged within the Toxicology scientific community and is further supported by the existing epidemiological evidence from well-conducted studies that showed no causal relationship between workers exposure to TiO2 and the development of lung tumours.
Animal Data suggest that lung tumours associated exposure to Titanium Dioxide are only observed at inhalation doses high enough to overwhelm lung clearance mechanisms resulting in particle deposition, lung overload and subsequent toxicity leading to tumour formation; these conditions are not relevant for normal exposure conditions. At inhalation doses that do not overwhelm normal pulmonary clearance mechanisms (as recommended for selections of maximum dose in OECD guidelines 451/116), no evidence for increased lung cancer risk is identified for several animal models, including rats, mice and

hamsters. The conclusion by ANSES to classify TiO2 as a presumed human carcinogen (Carc 1B) by the inhalation route is based solely on evidence in one single species (rats) which is the species most susceptible to developing lung tumours under conditions of lung overload. Regarding such conditions of lung overload (1) OECD indicates that they can lead to false positive and compromise the validity of inhalation carcinogenicity studies, and (2) they can be considered not to be representative of normal human exposure conditions, including at the work place. Finally, these tumours were observed only in rats, i.e. the species most susceptible to producing lung tumours under lung overload conditions.
As is widely recognized, the relevance of lung tumours induced in rats by inert, poorly soluble particles under exposure conditions associated with lung overload, as a predictor of a carcinogenic potential in humans is highly questionable. The chronic inhalation studies in rodents show dose-related pulmonary responses to TiO2.
Furthermore, the in vitro and in vivo studies performed following inhalation or intratracheal instillation of TiO2 support a secondary genotoxic mechanism through DNA oxidative damage due to the generation of reactive oxygen species. Such secondary mechanisms of genotoxicity represent non-specific mechanisms sustained by local inflammation observed at high dose levels which are not relevant to potential human exposure scenarios.
As a consequence, considering all available scientific evidence, there is in our view no robust scientific justification for a TiO2 classification as Carc. 1B – H350i by inhalation exposure route based on the CLP classification criteria. To this end, Cosmetics Europe supports comments made by TDMA that the classification of TiO2 as Carc. 1B – H350i by inhalation exposure route is not justified.

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ECHA note – A non confidential attachment was submitted with the comment above. TiO2_CE input CLHPublic consultation 14072016.pdf

Dossier Submitter's Response
See points 2, 3 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	TDMA/TDIC	BehalfOfAnOrganisation	333

Comment received

The following represents a commentary section-by-section, paragraph-by-paragraph according to the sequence of the CLH report as they were considered relevant for challenging the proposed classification. Failure to comment on a specific issue or study should not be deemed to accept the CLH report's discussion of the same.

Section 4.1.1.1, page 19-20 (carcinogenicity: oral):

NCI (1979; doses used 0; 25,000; 50,000 ppm in feed) reports slight increases in C-Cell adenoma and C-cell carcinoma only in female Fischer 344 rats, whereas in male Fischer 344 rats as well as in male and female mice, there was no statistically significant increase in tumours at all. The CLH report cites the review of this study from 1978, where only "one reviewer" felt that a firm conclusion could not be drawn about the carcinogenicity in Fischer 344 rats. To this, we note that IARC concludes that "oral, subcutaneous and intraperitoneal administration did not produce a significant increase in the frequency of any type of tumour in mice or rats." Given that IARC is cited in the CLH report more than thirty times throughout the document (but not in this section), it would appear appropriate to make explicit reference to their negative conclusion with respect to the oral route.

It is also noteworthy that EFSA last reviewed and published their assessment in 2004, and concluded as follows: "Increased incidences of thyroid C-cell adenomas or carcinomas were observed in female rats but these increases were neither statistically significant nor considered to be related to administration of the test compound". We note here that EFSA undertook another recent review in 2015, the outcome of which is due for publication in 2016.

Next, the discussed effect seen in the NCI (1979) study on the thyroid was only observed in female rats, but there was no associated thyroid follicular effect in male rats, which tend to be the more sensitive sex for follicular cell hypertrophy and neoplasia (Keenan, 2009), thus rendering this finding as somewhat implausible.

Further, from a scientific perspective, any identification of a cancer hazard based on a certain tumour incidence should take historical control data into consideration. For example, a publication reporting historical control data over a 20 year period (Tennekes et al., 2004) gives ranges of spontaneous tumour incidences of C-cell adenoma and carcinoma in female F344 rats which indeed correspond to the incidences reported by NCI (1979).

Finally, we note that thyroid tumour types may cause differential diagnostic problems when distinguishing between adenomas and carcinomas, requiring the use of additional immunohistochemical markers (Schmid, 2015), which were not yet in place at the time of conduct of the 1979 study, so that misclassification or interpretation with respect to adenoma/carcinoma cannot be ruled out.

Page 21, Section 4.1.1.2 Carcinogenicity: Inhalation – Incidences of tumours at the highest dose – 250 mg/m³ in the Lee et al (1985) study:

The findings of lung tumours at 250 mg/m³ described in the Lee et al. (exposure concentrations used: 0; 10; 50; 250 mg/m3, 6h/d, 5d/w) study clearly exceeded the maximum tolerable dose (MTD) and therefore it would be inappropriate to be considered as a positive tumour response.

According to the NIOSH Executive Summary of their Current Intelligence bulletin (NIOSH 2011, pages VI-VII), the 250 mg/m³ concentration in the Lee et al., 1985 study was an excessive dose and is not relevant for human risk assessment: "However, exposure concentrations greater than 100 mg/m3 are generally not considered acceptable inhalation toxicology practice today. Consequently, in a weight-of-evidence analysis, NIOSH questions the relevance of the 250 mg/m3 dose for classifying exposure to TiO2 as a carcinogenic hazard to workers and therefore, concludes that there are insufficient data at this time to classify tine TiO2 as a potential occupational carcinogen."

Lee et al (1985) noted that, due to excessive loading in the lungs of rats exposed chronically at 250 mg/m³, the lung tumours were different from common human lung cancers in terms of tumour type, anatomic location, tumorigenesis and were devoid of tumour metastasis. Therefore, the biological relevance of these lung tumours were negligible.

Table 1: Lung Tissue Analysis of TiO2

Exposure time
(months) Sex 0mg/m3 10mg/m3 50mg/m3 250mg/m3
TiO2 in dried lung tissue (%)
3 M ND 0.60 3.07 12.6
F ND 0.60 3.12 13.7
6 M ND 1.28 6.97 17.9
F ND 0.88 7.02 18.0
12 M ND 1.97 8.37 16.6
F ND 2.14 7.84 17.2
24 M ND 3.2 10.7 31.5
F ND 3.0 8.41 24.4

Table 2: Statistical analysis of Lung Weights (average TiO2 weights per lung at different exposure intervals)

Exposure time
(months) Sex 0mg/m3 10mg/m3 50mg/m3 250mg/m3
TiO2 weight (mg/lung)
3 M ND 2.5 21.7 180.8
F ND 2.8 16.6 136.8
6 M ND 4.8 57.3 275.3
F ND 4.4 54.0 238.6
12 M ND 10.1 75.6 361.7
F ND 8.7 59.7 381.5
24 M ND 20.7 118.3 784.8
F ND 32.3 130.0 545.8

Lung burdens of 118 and 130 mg/lung of TiO2 in male and female rats exposed to 50 mg/m³ TiO2 for 2 years did not result in lung tumours. In their Current Intelligence Bulletin document, NIOSH (2011) questioned/dismissed the relevance of the results following the exposures to 250 mg/m³ of the 2-year study. Moreover, Lee et al.

commented that the relevance of these rat tumours for humans was negligible, due to anatomic type, location, etc. Moreover, at the 50 mg/m3 exposure levels, there were no tumours in either male or female rats and this represented 118 mg/lung in the males and 130 mg/lung in the females. Therefore this study should not be considered a positive study for carcinogenicity, but instead a negative study for carcinogenicity in rats.

Page 21, Section 4.1.1.2 Carcinogenicity: Inhalation - quality assessment of the Lee et al (1985) study with regard to its adequacy for classification purposes:

The Lee et al. (1985) study used test item concentrations of 0, 10, 50, 250 mg/m³ for the chronic whole body inhalation exposure towards pigmentary titanium dioxide. For the evaluation of that study in the context of a carcinogenicity classification, its adequacy for this purpose needs to be evaluated. Adequacy defines the usefulness of information for the purpose of hazard identification and risk characterisation; in other words whether the available information allows clear decision-making about whether the substance meets the criteria for classification. Since the adverse findings in rats were obtained at doses exceeding the maximum tolerated dose, the adequacy of that study for classification purposes is explicitly questioned – to demonstrate this, the study design of Lee et al. was checked against the relevant OECD and ECHA guidance documents:

1) The guideline OECD 451 for the conduct of carcinogenicity studies, in conjunction with the relevant OECD guidance document 116, highlights on various occasions that inhalation concentrations overwhelming physiological mechanisms are in exceedance of the MTD:

a) The guidance explicitly states that "inhalation of doses that overwhelm pulmonary clearance may lead to tissue responses that are specific to the species being tested" (section 94, p.54).

b) "The robustness of a carcinogenicity or chronic toxicity study, in particular the former, is dependent on a demonstration that the dose levels selected in the study are adequate to show an effect or effects of the test substance, without producing either false negative results (because the doses selected were too low) or false positive results (because metabolic/homeostatic mechanisms are overwhelmed, etc.), which may be problematic in assessing risk in humans" (section 101, page 55).

c) In the selection of the maximum concentration, it should be considered that "disturbances of physiology or homeostasis that would compromise the validity of the study should be considered in the dose-selection process. Examples include hypotension, inhibition of blood clotting, overwhelming normal pulmonary clearance mechanisms, immune system effects, and in some cases hormonal imbalance" (p.63).

d) "For substances likely to accumulate in the lung over time due to poor solubility or other properties, the degree of lung-overload and delay in clearance needs to be estimated based on adequately designed pre-studies; ideally a 90-day study with post-exposure periods long enough to encompass at least one elimination half-time. The use of concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged" (section 135, p.71).

2) The ECHA guidance on the Application of the CLP Criteria (Version 4.1, June 2015) highlights that "Tumours occurring only at excessive doses associated with severe toxicity

generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard" (section 3.6.2.3.2., p.379-380).

The highest concentration used in the Lee et al. study clearly exceeded the MTD, since lung overload conditions were already attained at the mid concentration of 50 mg/m³, as cited in the publication of the study director (Lee et al. 1986):

"Lung response at 10 mg/m³ satisfied the biological criteria for a "nuisance dust," while adverse effects resulting from gradually accumulated particles (8.1%, 67.7 mg per lung) were found after 1 year of exposure to 50 mg/m³. An early pulmonary response indicating an overloaded lung clearance mechanism was manifested by massive accumulation of dust-laden macrophages (dust cells), foamy dust cells, free particles or cellular debris derived from disintegrated foamy dust cells in the alveoli adjacent to the alveolar ducts. Alveolar proteinosis also appeared to be an important marker of an overloaded lung clearance mechanism and was observed at 50 and 250 mg/m³ after 1 year of exposure."

Page 23, Table 4.1.1.2-03 (Comments on re-evaluation of the Lee et al. (1985) tumours):

To further characterise the broncho-alveolar lesions, in 1992, a group of pathologists from North America and Europe examined lung lesions produced by para-aramid RFP (respirable fibre-shaped particles) and titanium dioxide .This panel diagnosed the lesion as a "proliferative keratin cyst" (PKC). Additionally, the pathologists agreed that the lesion was not a malignant neoplasm and is most likely not neoplastic. A minority opinion was that the lesion is probably a benign tumour (Carlton 1994; Levy 1994). Another subsequent international pathology workshop was convened to develop standardized histological criteria for classifying pulmonary keratin lesions (Boorman et al., 1996). As a consequence, most of the lesions that had originally been diagnosed as "cystic keratinizing squamous cell carcinomas" were re-classified by the consensus panels as non-tumorous "proliferative keratin cysts" (Warheit and Frame, 2006).

In the aftermath of two international pathology workshops designed, in part, to establish histological criteria for classifying pulmonary keratin lesions, these lesions were evaluated by four pathologists using current diagnostic criteria. Microscopic review of 16 proliferative squamous lesions, previously diagnosed as cystic keratinizing squamous cell carcinoma in the lungs of rats from the 2-year inhalation study was performed. Unanimous agreement was reached as to the diagnosis of each of the lesions. Two of the lesions were diagnosed as squamous metaplasia and 1 as poorly-keratinizing squamous cell carcinoma. Most of the remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts (Warheit and Frame, 2006).

Consequently, the diagnosis of many of these lesions has changed after the development of revised criteria. Hence, relying on the previous analysis by the study author is not a reliable basis for classification.

Page 24 – Comments on the study by Heinrich (1995), Female Wistar rats and NMRI mice were exposed whole body to aerosols of P25 TiO2:

This study by Heinrich et al. (single exposure concentration: 7.2 mg/m3 1-4 months, 14.8 mg/m3 5-8 months, 9.4 mg/m3 9-24 months, 18h/d, 5d/w) was noted as a reliability 3

study because it was a satellite group used for another study. The study included only female rats and mice and did not have a dose response paradigm. In addition, the rats and mice were exposed for 18 hours/day, 5 days per week for 24 months (rats) or 13.5 months (mice). The tumour response of mice was not significantly different from controls. Moreover, the evaluation of tumours (including malignant tumours) was assessed and did not consider the two international lung pathology workshops – which have reassessed the criteria for describing malignant vs. benign tumours – particularly with reference to the cystic keratinizing pulmonary squamous cell lesions that are unique to the rat.

Consequently, the diagnosis should have changed after reconsideration of the revised criteria.

Page 26 – Comment on the studies by Muhle (1989, 1991, 1995):

Muhle employed only a single exposure concentration: 5 mg/m3 (6h/d, 5d/w). This was a negative study that should be used in an overall weight-of-evidence consideration – and clearly is more physiologically relevant than the Pott and Roller (2005), Xu et al. (2010) and Yokohira et al. (2009) studies – which were conducted using a non-physiological routes of exposure (intratracheal instillation).

These intratracheal instillation studies utilised excessive doses (Pott and Roller) or non-standard routes of administration and should therefore not be considered for classification purposes.

Pages 26, 27 29: Comments on the studies by Xu et al, Yokohira et al. and Muhle et al.:

The CLH report indicates that negative results from the Muhle et al. 1989, 1991, 1995 (p. 26-27) chronic inhalation study in rats with titanium dioxide were not sufficient to adequately assess a carcinogenic potential because it was conducted at concentrations lower than studies with positive findings. The study failed to identify any toxicological or carcinogenic response in the exposed rats and is thus important in this regard and also because significant titanium dioxide was retained in the lung amounting to 2.72 mg/lung after 24 months.

Although discounting the Muhle et al. study because of the lower exposure concentration used, the CLH report implicate fibrosis and bronchioalveolar hyperplasia as precursors of a carcinogenic response. In fact, fibrosis was present in the controls at a comparable rate to that of titanium dioxide exposed rats. Fibrosis in titanium dioxide exposed rats was minimal to mild and not statistically significantly different from controls (Muhle et al., 1991). While dismissing the Muhle et al. studies as insufficient evidence for a carcinogenic response, the CLH report inappropriately uses the same study to imply a carcinogenic response due to mild and statistically insignificant changes in fibrosis and hyperplasia.

There are two additional papers referenced in the CLH report as supportive and that involve the use of intra-tracheal administration (p. 27-30). Xu et al. (2010) dosed HRas female transgenic rats multiple times by intra-tracheal instillation (dosages used: 125 and 250 ug/rat once every 2 weeks in weeks 4-16) and observed increased DHPN-induced alveolar cell hyperplasia and adenomas in the lung at the two doses administered. In a second similar study with HRas transgenic male rats (Yokohira et al., 2009; dosages used: 0.5 mg/rat, once) indicated that neither "micro" sized nor "nano" sized titanium dioxide caused any increased inflammatory changes or increased rates of adenomas / carcinomas after a single intra-tracheal administration.

The CLH report accepts that there is little experience with the HRas rat model and intra-tracheal administration. Importantly, there were no lung lesions without pretreatment with DHNP.

Pages 30-32 – Comments on the study by Pott and Roller (2005):

Because of the experimental design, the 19 dust study (DS) data for female rats cannot be interpreted in a manner that makes them useful for human risk assessment and development of airborne dusts limits in workplace environments. Likewise, because of the species (rat) and the exposure conditions (particle overload in the lungs), the data are not applicable to hazard classification of granular biopersistent particles (GBP) as to human carcinogenicity. Problems with interpretation of the 19-DS experiments include:

1. Dosages used: P25 (5 x 3mg/rat, 5 x6 mg/rat, or 10 x 6mg/rat); P805 (15 x 0.5 mg/rat, or 30 x 0.5 mg/rat); micro-TiO2 (10 x 6 mg/rat, or 20 x 6 mg/rat)

2. The high doses and the high dose-rate delivery led to lung overload in the rats. 19-DS lung instillations were performed in a dose range that lacks relevance to the actual exposure that occur at workplaces. [TiO2 anatase – instilled mass = 120 mg into lungs; TiO2 hydrophilic ultrafine (UF) – 60 mg into lungs; TiO2 hydrophobic – 15 mg into lungs].

3. The responses of rat lungs to overload conditions are unique to this species and not particle-specific.

4. The 19-DS did not include low-dose studies andonly female rats were employed. The rat-lung inflammatory response has a mechanistic threshold.

5. The occupational epidemiology results for workers in dusty trades experiencing historically elevated levels of airborne dust do not bear out the tumorigenicity of GBP, as might be predicted from the 19-DS results.

Using the same dusts administered as single doses to rats by intratracheal instillation, but at lower doses corresponding to permissible workplace levels, Rehn et al. (2003; dosages used: P25 and T805 (0.15, 0.3 0.6 and 1.2 mg/rat) evaluated the lungs at 3, 21, or 90 days post-exposure by bronchoalveolar lavage to gauge the lung inflammatory and genotoxic reactions. Quartz particles were used as a positive control. The authors concluded that both types of TiO2 were not different from saline controls.

Section 4.1.1.3, page 33-34 (carcinogenicity: other routes):

This section reviews three studies with intraperitoneal administration, and one study with subcutaneous injection, all of which produced a negative response for carcinogenicity. Whereas there are obvious limitations in all four of these studies, this is also the case with other studies mentioned in the CLH report, which are characterised as not providing sufficient accumulation to elicit a carcinogenic response. Further, there are no conclusions being taken forward to section 4.1.4.

Section 4.1.1.4, page 48 (carcinogenicity: dermal):

The CLH report states that the SCCS Opinion of 2013 (published in 2014) concludes on a

lack of penetration of TiO2 through the dermis. It then however speculates without scientific reasoning that "it remains somewhat uncertain if particles can penetrate through damaged skin or during repeated or long term applications, since a number of studies have indicated that TiO2 nanoparticles can enter the hair follicles and sweat glands".

This is an incorrect interpretation of the results reflected in the Scientific Committee on Consumer Safety (SCCS) opinion. In contrast, from a whole series of dermal absorption studies in rat and human skin, SCCS quite rightly concludes that:

- Neither the shape nor the surface chemistry seem to influence NP penetration after acute and subacute exposure; all different TiO2 NP types applied on skin areas of human forearm have only been detected on the outermost layer of the stratum corneum irrespective of their surface chemistry, nano-particle (NP) size and shape (see for example: Pflücker et al., 2001; Schulz et al., 2002).

- Several investigations have failed to demonstrate a role for hair follicles as a percutaneous absorption pathway. In fact, Ti was detected in the stratum corneum and in the follicle channels, but not in the interfollicular space under the stratum corneum or into the viable layers of the forearm skin of human volunteers (see for example: Menzel et al., 2004; Lademann et al., 1999).

In conclusion, there is no animal evidence of carcinogenicity via dermal exposure. There are no human epidemiological (dermal) studies, but estimates exist indicating the reduction in skin cancer cases due to decades of sunscreen use containing TiO2 (such as Gordon et al 2009; van der Pols et al, 2006). Experimental evidence is clear beyond doubt that TiO2 does not penetrate beyond the stratum corneum.

Section 4.1.2, page 38-41 (human information):

Whereas the CLH report acknowledges that human epidemiological data do not indicate a link between human exposure to TiO2 and cancer, preference is given instead to lung tumours developing in female rats only under conditions of excessive lung overload with PSPs of low cytotoxicity.

The relevance of the cited epidemiological studies is downplayed because of claimed "methodological limitations" and "misclassification of exposure". It is our opinion that the stated limitations are either only minor or even irrelevant, and do not effectively leave the conclusion of these studies in doubt.

What is of major concern is that the CLH report without obvious reason does not mention the recent cohort study (Ellis et al, 2010; Ellis et al, 2013) of TiO2 manufacturing workers (involving > 5000 workers), which like all other previous studies does not indicate any association between TiO2 exposure and human lung cancer. In total, all available human cohort studies amount to a worker population of more than 24,000.

The available, unequivocally negative epidemiological data for TiO2 and other negative epidemiological data with poorly soluble particles such as coal mining dust should be given the weight that the CLP regulation (Annex I, section 1.1.1.4) assigns to them.

Section 4.1.4, page p. 46-65 (summary and discussion of carcinogenicity):

Page 47, 2nd paragraph (suggested accumulation of TiO2 in organs): in this section, the

CLH report cites as supportive information publications by Sheng et al. (2013) and Gui et al. (2013). As to the latter, TDMA/TDIC are aware that the publication by Gui et al. (Particle and Fibre Toxicology, 2013) has been retracted by the publishing journal. It was found after an investigation by a committee at Soochow University (China) that incorrect statistical methods were used; there were measurement errors in determining 8-OHdG concentrations; and that original data was missing. The possibility that the paper by Sheng is also affected by similar errors cannot be ruled out.

The representation of some of the studies in the CLH report is not correct:

- In the study by Brun (2014), they attempted to define the level of dissolved titanium by X-ray absorption spectroscopy, but the concentrations were too low to be adequately analysed. They also concluded that the amount of TiO2-NPs in gut tissues was so low that they were unable to quantify it by particle-induced X-ray emission (local limit of detection: 20-30 ppm).

- As to the study by Jones (2015), the account of this in the CLH report is incorrect - in contrast to the value for oral absorption stated in the CLH report (i.e., <0.1%), there was no effect of dosing (5 mg/kg) on Ti levels in blood and urine; in fact, the authors themselves state contrastingly that "0.1 % absorption would have given rise to a demonstrable increase in Ti blood levels" – however, there was no measurable difference between treated and controls, so that absorption was even well below 0.1%.

- Cho (2013) dosed rats up to 1042 mg/kg bw/d for 13 weeks but in fact did not report "extremely low absorption"; instead, they clearly stated that Ti levels in all tissue samples showed no significant increase at any dose level, and the urinary excretion likewise was not significantly different from controls.

Finally, there are many other studies documenting the negligible oral absorption, which are not reviewed in the CLH report, such as:

- in vivo rat studies by Himmelstein (2014a,b; 2015) at a dose of 500 mg/kg bw with urinary, blood and tissue levels in the same range for treated and control animal, mostly close to or below detection limit.

- Langford-Pollard (2003) exposed rats via feed to 200ppm TiO2, and the levels of Ti in blood and tissues were mainly below detection limit.

- Janer et al. (2014) treated rats at 100 mg/kg bw Ti and there was no statistically significant increase in Ti levels in any of the tissues sampled compared to vehicle controls.

- Kim & Park (2014) administered 10 and 100 mg/kg bw/d to rats; there were no statistically significant increases of Ti levels in any of the organs sampled.

- Geraets et al. (2014) dosed rats at a dose of 6.8-8.6 mg/kg bw; analysis of liver and spleen tissue samples yielded titanium levels mostly below the limit of detection (twenty-eight measurements below LOD, one at LOD and only one above LOD). The authors concluded that "the results indicate that after oral administration absorption of TiO2 is very low."

- Wang et al. (2007; 2012) dosed rats for 30 days at up to 200 mg/kg bw/d, with no statistically significant differences in levels of titanium either in blood or in livers, kidneys or in spleen.

Overall, this section of the CLH report ignores a large body of evidence that the oral bioavailability of a wide range of different types and sizes of TiO2 material with an emphasis on nanomaterials, also partly involving very high doses, clearly documents the negligible absorption of TiO2 via the oral route.

Page 47, 2nd paragraph (toxicokinetic considerations): The reference Jovanovic (2015) is merely secondary review data published elsewhere, and should not be cited as an indication of primary peer-reviewed evidence. We consider the study by Tassinari et al. (2014) as invalid as their conclusions on absorption at a dose of 1 and 2 mg/kg bw are in clear contradiction to several other studies in animals and humans which involve doses two-three orders of magnitude higher, and which conclude that no appreciable absorption occurs based on the absence of any difference between tissue and or blood levels between dosed groups and controls. Finally, the study by Pele et al. (2015) does not provide evidence for systemic (particulate) absorption, because no Ti-specific particle analyses were performed, and is in contradiction to a large body of evidence documenting that the oral absorption of TiO2 is negligible.

Sections 4.1.1.1, p.19-20 (carcinogenicity, oral), 4.1.1.2, p.21- (carcinogenicity, inhalation), 4.1.1.3 (carcinogenicity: other routes) and 4.1.1.4 (carcinogenicity, dermal) (issue: systemic carcinogenicity), as well as 4.1.4 (conclusions): as a general comment there is a complete absence of any indication of systemic carcinogenicity after exposure to TiO2; the only carcinogenic responses are seen in the lungs of female rats only under conditions of excessive overload.

Page 47, 3rd paragraph (conclusion on oral carcinogenicity): The CLH report implies that there might be forms of TiO2 that are taken up better than those tested to date, which may lead to "accumulation of particles". A wide range of TiO2 (nano and non-nano) forms have been investigated for their potential for absorption after ingestion, which overwhelmingly yield the conclusion that the oral absorption is negligible to zero.

Page 50 (Concluding remarks):
"In conclusion, although no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data, lung tumours were reported in one inhalation study and one intra-tracheal study of acceptable quality. Carcinogenic potential was also reported in two further (inhalation or intra-tracheal) studies of lower reliability but of adequate relevance."

This statement is not appropriate for the following reasons:

1. The benign lung tumours reported in the Lee et al., (1985) study were known to occur at an exposure level, which exceeded the maximum tolerated dose (250 mg/m3). This was confirmed by NIOSH in their Executive Summary of their Current Intelligence Bulletin on titanium dioxide. Indeed, exposures of rats to aerosol concentrations of 50 mg/m3 for 2 years did not produce tumours.

2. The Pott and Roller (2005) intratracheal instillation study is cited as a study of acceptable quality, but was not properly evaluated in the CLH report. This is not a reliability R=2 study: it and utilises excessive doses (up to 120 mg dust/ lung), lacks dose-response, no physiological route of exposure and employs female test animals only

and therefore should not be used for hazard assessment.

3. The Heinrich et al (1995) study was reported as a lower reliability study. Rats and mice were exposed for 18 hours per day. The characterisation of tumours preceded the re-evaluation of rat tumour lung pathology workshops and would need to be reconsidered before determining whether these tumours were malignant. Heinrich (rated R3 in the CLH report) reported that 32/100 rats developed lung tumours after exposures to ultrafine TiO2. These included benign squamous tumours, 3 squamous cell carcinomas, adenomas and 13 adenocarcinomas. However, the publication of this report preceded the revised criteria based on 2 workshops for classification of cystic keratinizing squamous lesion of the rat lung. (Carlton, 1994; Levy 1994 and Boorman et al., 1996). As a consequence, the determination that these are malignant tumours should have been properly re-evaluated according to the new criteria.

4. The Xu et al. (2010) and Yokohira et al. (2009) studies utilised nonstandard models and a nonphysiological route of exposure. The findings from these studies would not be considered reliable for classification.

As a consequence, the only study that may be viewed as a reliable inhalation study did not give tumours in any of the test animals up to the MTD. Only when the maximum tolerated dose was grossly exceeded did female rats develop tumours, which were different from common human lung tumours in terms of tumour type, anatomic location, tumorigenesis and were devoid of tumour metastasis. It is noteworthy that this finding was not considered relevant for humans by NIOSH.

Accordingly, the TDMA/TDIC does not agree with the concluding remarks on page 50 of the CLH report because no adequate, sufficient or reliable information has been presented to warrant a classification of titanium dioxide for carcinogenicity.

Page 57-58 (role of phys-chem properties of TiO2, in particular shape):

On page 57 (8th paragraph) and page 58 (2nd paragraph), the CLH report states that "it might be hypothesized that elongated-like shapes would have a similar behaviour to fibres."

The titanium dioxide industry does not manufacture any fibrous products. Therefore, the hypothesis that elongated TiO2 shapes having a similar behaviour to fibres as speculated in the current CLH report is not substantiated in any way. In cases where there is clear evidence of the existence of such fibres, this should have been explicitly stated in the CLH report.

Page 57 – "The impact above show that coating can impact the toxicity of TiO2 and the inflammation response can differ between different forms although a clear pattern cannot be drawn from the existing data"

In comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations, the impact of surface treatments on particle toxicity was investigated (Warheit et al. 2005): rats were exposed by inhalation for 4 week to high concentrations ranging from 1130 - 1300 mg/m3 of TiO2 particle formulations with various surface treatments. The results from these studies demonstrated that at extremely high concentrations only the TiO2 particle formulations with the largest components of both alumina and amorphous silica surface treatments produced mildly

adverse pulmonary effects when compared to the base reference TiO2 control particles

Page 58-60 (carcinogenic mode of action, hypothesised DNA interaction): The CLH report cites several publications seemingly reporting the presence of TiO2 NPs within cell nuclei. However, the possibility that these particles are either overlying the nucleus in the sections used or were transferred from cytoplasm to nucleus during sectioning (as is considered highly likely by experts in this technique) is very likely. In all reviewed papers, there is no direct evidence of NPs binding to DNA. Even if particles do penetrate the nucleus, oxidative damage is the only established genotoxic consequence of exposure to TiO2 NPs. Within the Nanogenotox (2013) programme, extensive transgenic mouse testing was conducted, based upon which a clear absence of primary genotoxic effects can clearly be ruled out.

In essence, there is no evidence backing the speculation that TiO2 might inflict direct DNA damage. It is thus considered inappropriate to argue in favour of a potential involvement of direct DNA reactivity in the carcinogenicity classification, and these speculations in the CLH report should therefore be disregarded. This is also in our opinion reflected by the fact that the previously announced classification report for germ cell mutagenicity has in the meantime been withdrawn (based on a lack of scientific evidence).

Page 61, 3rd paragraph (Interspecies variations in experimental animals): after an extensive discussion of very clear and distinct interspecies differences, the CLH report surprisingly finally concludes here that "Therefore the risk of several known human particulate carcinogens would be underestimated by using dose-response data and hazard properties from rodent models other than rats"

This statement is in contradiction to the scientific evidence presented before, and not supported by any scientific evidence. When considering interspecies differences to particle overload of PSPs of low cytotoxicity in general and TiO2 in particular, the rat is a uniquely sensitive species when compared to other rodent species (mouse and hamster) (ECETOC, 2013; ILSI, 2000). Moreover, when comparing the response of rats to nonhuman primates and coal mine workers, the rat response to particle overload is obviously hyper-responsive and the particle disposition is significantly different from the other species. In nonhuman primates and humans, inhaled particles translocate to a much greater extent to the interstitium, and the pulmonary responses are significantly reduced when compared to the rat pulmonary responses (Nikula et al. 2001).

Page 61, 3rd paragraph (Interspecies variations in experimental animals): the CLH report states that "Finally, although no lung tumour was found in mice and hamsters, they are known to give false negatives to a greater extent than rats in bioassays for some particulates that have been classified by IARC as human carcinogens (limited or sufficient evidence), including crystalline silica and nickel subsulfide. The lung tumour response to other known human particulate carcinogens (such as tobacco smoke, asbestos, diesel exhaust…) is significantly less in mice than in rats. Therefore, the risk of several human particulate carcinogens would be underestimated by using dose-response data and hazard properties from rodent models other than rats".

The relevance of particle-overload related lung tumours in rats for human risk assessment following chronic inhalation exposures to poorly soluble particulates (PSP) of low cytotoxicity has been a controversial issue for more than 30 years. In 1998, an ILSI (International Life Sciences) Working Group of health scientists was convened to address

this issue of applicability of experimental study findings of lung neoplasms in rats for lifetime-exposed production workers (ILSI, 2000). A full consensus view was not reached by the Workshop participants, but it was generally acknowledged that the findings of lung tumours in rats following chronic inhalation, particle-overload PSP exposures were unique to rats; and that there was an absence of lung cancers in PSP-exposed production workers. Subsequently following up on this, a further thorough and comprehensive review of the health effects literature on poorly soluble particles/lung overload was published by an ECETOC Task Force in 2013. One of the significant conclusions derived from that technical report specified that the rat represents a uniquely sensitive lung tumour model under chronic inhalation overload exposures to PSPs of low cytotoxicity.

Page 61, 5th paragraph (extrapolation to humans): the CLH report states that "Furthermore, humans and rats display some consistency in response to dust exposure: inflammatory reaction with fibrosis at high concentrations".

This is a misleading interpretation of scientific evidence, and the conclusion reached in the CLH report is not backed up by any supporting data.

Instead, in conditions of heavy exposure of humans to PSPs of low cytotoxicity (such as in coal miners), inhaled particles are translocated to a large extent to the interstitium, wherein they can respond with only limited inflammation and some fibrosis (coal workers pneumoconiosis). On the contrary, rats exposed to high doses of such PSPs (TiO2 and carbon black (CB)), particles remain primarily in alveolar ducts and showed more severe intra-alveolar acute inflammation, as a prelude to tumours.

Page 61, 4th and 5th paragraph and page 62, 1st paragraph (extrapolation to humans): Here, the CLH report states (among others) the following:

"The relevance of rat model predicting human response to inhaled particles is the subject of controversial discussion. A comparison of lung tumor types in rats and humans and the relevance of rat model in risk assessment are well described by the NIOSH (2011)"

"...particles that deposit in this region can translocate into the interstitium where they can elicit inflammatory and fibrotic response. Furthermore, humans and rats display some consistency in response to dust exposure: inflammatory reaction with fibrosis at high concentrations."

"On the contrary, rats showed more sever intra-alveolar acute inflammation, lipoproteinosis and alveolar epithelial hyperplasia response than humans when they were chronically exposed to silica, talc, or coal dust."

"Thus, the overload concept seems to be also relevant for humans, and in particular for workers exposed to high dust exposure."

This section gives an inaccurate interpretation regarding the relevance of lung tumour responses in particle overload-exposed rats when compared with humans. The lack of relevance of rat lung tumours following chronic inhalation exposures to PSPs of low cytotoxicity can be summarised by the following five factors:

1. Data and findings from three subchronic, 90-day interspecies rodent inhalation studies provide convincing mechanistic justifications to better understand the distinct differences in cellular responses to particle overload exposures when comparing rats to either mice or

hamsters (Bermudez et al., 2002; Bermudez et al., 2004; Elder et al., 2005; Carter et al., 2006). In addition, a conceptual AOP scenario has been developed (ECETOC, 2013) for the rat pulmonary response to particle-overload, leading to lung tumours which is substantively different from pulmonary responses demonstrated in particle-exposed mice or hamsters and/or in either nonhuman primates or coal workers. In chronic inhalation studies to TiO2 and carbon black particles, only rats developed tumours – but not mice exposed to the same particles/concentrations.

2. Several 2-year inhalation studies have compared the effects of similarly or identically exposed rats and monkeys to a variety of low solubility dusts, such as shale dust, petroleum coke dust and diesel exhaust particles (Wagner et al., 1969; Klonne et al, 1987; Lewis et al., 1989; MacFarland et al., 1982; Nikula et al., 1997; Nikula et al., 2000). In every case, the lung cellular responses of rats exposed chronically to particles were considered hyperinflammatory and hyperplastic, while the pulmonary responses in monkeys were limited to general, normal physiological effects (particle accumulation, macrophage responses) to inhaled particles. In addition, morphometric studies reported by Nikula et al., 1997 were developed to investigate the distribution patterns of inhaled particles in both chronically-exposed rats and cynomolgus monkeys. The results demonstrated that the majority of inhaled particles that deposited in the distal regions of the lung had transmigrated to interstitial compartments of the lungs of nonhuman primates. In contrast to the pulmonary responses and particle distribution patterns measured in monkeys, inhaled particles in diesel and coal dust exposed rats after deposition were retained primarily on alveolar surfaces, and subsequently stimulated active inflammatory responses. In another set of morphometric studies assessing the particle disposition pattern in deceased coal miners, particle distribution patterns similar to cynomolgus monkeys were measured. In this regard, most of the coal particles had translocated to interstitial sites (Nikula et al., 2001).

3. The ICRP – Human Respiratory Tract Model has been an internationally recognised standard model to estimate the deposition, clearance and retention patterns for workers in the nuclear and coal dust industry (ICRP, 1994). The model has been updated/revised by Gregoratto et al. (2010; 2011) to demonstrate that a greater proportion of inhaled low solubility dusts translocate from alveolar/respiratory bronchiolar sites of initial particle deposition to interstitial sites. This updated revision has important implications for lung clearance and retention estimates of inhaled particles, and supports species differences in particle distribution patterns, in particular the finding of enhanced translocation of inhaled particles to the interstitium. The impact of the model supports increases in the retention time of particles in the human lung. It is also noteworthy that the finding of enhanced transmigration rates in these models also correlates well with the morphometric findings reported by Nikula et al. (2001) in particle-exposed lungs of nonhuman primates and coal workers.

4. Fundamental differences have been recognised by human and veterinary pathologists when considering the characterisation and location of tumour types in rats chronically exposed to PSPs of low cytotoxicity vs. humans exposed to cigarette smoke or asbestos fibres (Schultz, 1996; Green, 2000). First, many PSP-induced rat neoplasms are unique species-specific entities that are only consistently observed in particle overload instances. Furthermore, there is no known documentation of human production workers developing an increase in lung cancers following exposure to poorly soluble particulates. Moreover, the types of lung tumours characterised in humans exposed to cigarette smoke or asbestos fibres – occur primarily in the bronchiolar regions of the respiratory tract and do not have the "squamous or keratinising" features of rat lung tumours, which are more prominent in this region of the lung following chronic exposures to such PSPs. It is generally acknowledged that comparing asbestos and cigarette smoke-induced tumours in

humans to such PSP-induced neoplastic entities in the rat probably does not contribute meaningfully to cancer risk of such PSPs, as the lungs differ in morphological aspects such as the presence (humans) and absence (rodents) of a respiratory bronchiole (Schultz, 1996). Nonetheless, it should be recognised that cystic keratinising tumours of rats arise very differently than squamous lesions in humans and appear to be adaptive versus true neoplastic changes (Carlton, 1994; Levy, 1994). In the Lee et al. study 1985 – in which rats developed tumours after being exposed to 250 mg/m3 (but not at 50 mg/m3), it was noted by Lee that the lung tumours were different from common human lung cancers in terms of tumour type, anatomic location, tumorigenesis and were devoid of tumour metastases. Therefore, these lung tumours were deemed biologically irrelevant.

5. All of the published epidemiological studies on titanium dioxide (Boffetta et al. 2004; Chen and Fayerweather, 1988' Ellis et al., 2010 and 2013; and Fryzek et al. 2003), carbon black and toner production workers demonstrate no association between working life-time exposures to PSPs of low cytotoxicity and lung cancer and/or non-cancer respiratory disease.

Page 62, 1st paragraph (extrapolation to humans): the CLH report argues that "In addition, lung overload after TiO2 inhalation is characterized among other by lipoproteinosis, fibrosis and metaplasia in rats. Although these effects were not observed in mice and hamsters (Bermudez et al., 2002), these lesions have been reported in humans exposed to TiO2."

This statement is not correct, since these effects have not been reported in humans. In contrast, the Chen and Fayerweather study concludes that exposure to TiO2 in production workers is not correlated with lung tumours or other respiratory effects.

Page 62, 1st paragraph (extrapolation to humans): the CLH report then concludes that ". it appears that lung retention and chronic pulmonary inflammation are more consistent with the findings in rats than in mice and hamsters. Thus, the overload concept seems to be also relevant for humans, and in particular for workers exposed to high dust exposure."

This conclusion is in contradiction to current scientific knowledge: the assessment of the lungs of human coal mine workers demonstrate entirely different biokinetic patterns when comparing the disposition of dusts in the lower respiratory tracts of rats and humans. In rats, the inhaled particles remain primarily in the alveolar duct regions and under particle overload conditions, generate hyperinflammatory responses. Contrastingly, in nonhuman primates and coal mine dust workers, a much greater proportion of the inhaled particles translocate to interstitial sites, and the pulmonary response is significantly decreased when compared to rats (Nikula et al., 2001).

Page 62, 2nd paragraph (extrapolation to humans): in this paragraph, the following statements are considered inappropriate:

"Controversy exists over the biological significance of cystic keratinizing squamous cell tumours, which developed in response to chronic inhalation of diverse particulate materials, and their relevance to humans. In fact, this type of lesion appear to be a unique rat (sic) tumour occurring under exaggerated exposure conditions."

"These lesions have not been reported in the literature in mice or hamsters exposed to

dust under similar conditions and have not usually been seen in humans."

"In summary, at this time, the relevance of these tumors to man remain unclear."

The suggested unclear relevance is disputed: fundamental differences have been recognised by human and veterinary pathologists when considering the characterisation and location of tumour types in rats chronically exposed to PSPs of low cytotoxicity vs. humans exposed to cigarette smoke or asbestos fibres. First, many PSP-induced rat neoplasms are unique species-specific entities that are only consistently observed in particle overload instances. Furthermore, there is no known documentation of human production workers developing lung cancers following exposure to poorly soluble particulates. Moreover, the types of lung tumours characterised in humans exposed to cigarette smoke or asbestos fibres – occur primarily in the bronchiolar regions of the respiratory tract and do not have the "squamous or keratinising" features of rat lung tumours which are more prominent in this regions of the lung following chronic exposures to PSPs of low cytotoxicity. It generally is acknowledged that comparing asbestos and cigarette smoke-induced tumours in humans to PSP-induced neoplastic entities in the rat does not contribute meaningfully to cancer risk of such PSPs, as the lungs differ in morphological aspects such as the presence (humans) and absence (rodents) of a respiratory bronchiole. Nonetheless, it should be recognised that cystic keratinising tumours of rats arise very differently than squamous lesions in humans and appear to be adaptive versus true neoplastic changes.

Page 63, 3rd paragraph (extrapolation to humans): it is finally concluded in the CLH report that "Expert advisory panels have concluded that chronic inhalation studies in rats are the most appropriate tests for predicting the inhalation hazard and risk of fibres to humans. In absence of mechanistic data to the contrary, the rat model is adequate to identify potential carcinogenic hazards of poorly soluble particles to humans, such as TiO2"

We contend that whereas the rat may be the preferred model to gauge the potential chronic hazards of inhaled low solubility materials, it is untrue and inaccurate to assume that these tests include the assessment of risks of inhaled materials to humans. A broad number of investigators have clearly questioned the relevance of the rat model for identifying the risks of inhaled low solubility particulates.

Section 4.1.4, page 63-65 (assessment by scientific and regulatory bodies):

The consideration of the IARC assessment in the CLH report needs to be put into the following context:

The IARC Working Group concluded in 2006 that there was sufficient evidence that TiO2 is carcinogenic in experimental animals based on a similar dataset (except Xu et al. (2010) (IARC, 2006). In their assessment, the IARC Working Group re-evaluated carcinogenic hazards of three different, low toxicity, poorly soluble particles (PSP) of low cytotoxicity, namely titanium dioxide, carbon black and talc particles (IARC, 2010). In its preamble, IARC maintains that its monographs represent the first step in "carcinogen risk assessment" making a distinction between cancer hazard and risk and emphasizing that the Monographs identify cancer hazards even when risks are very low at current exposures (IARC, 1996).

The IARC classification scheme has limited utility for identifying PSP of low cytotoxicity

carcinogenic risk in humans, particularly when a clearly identifiable discrepancy exists between experimental carcinogenicity results in a uniquely sensitive species (i.e., the rat) – contrasted both with the results of experimental inhalation studies in monkeys, and numerous epidemiology findings in highly exposed production workers. In addition, the validity of the epidemiology findings in PSP-exposed humans is substantiated when considering other approaches to particle inhalation kinetics and responses in nonhuman primates and humans. These include 1) histopathological/morphometric findings in the lungs of nonhuman primates and coal workers demonstrating a significantly different biokinetic/particle distribution pattern of inhaled dusts compared to exposed rats (i.e., greater translocation of particles to interstitial sites in monkeys/humans vs. rats – whereas inhaled/deposited particles remain within lung macrophages on alveolar surfaces (Nikula et al., 2000; 2001); and 2) confirmation of significantly enhanced particle transmigration to interstitial sites in humans, using newly updated ICRP modelling (Gregoratto et al. 2010; 2011). Accordingly, these findings employing totally different approaches provide convergent results with the epidemiological conclusions which demonstrate an absence of neoplastic effects in particle-exposed humans.

The conclusion of a questionable relevance and appropriateness of using rat data as a model for the estimation of human neoplastic pulmonary response has been recognised previously by other scientific committees, which had taken the view that the rat lung tumours are unique to that species under certain exposure conditions. Indeed the Presidential and Congressional Commission on Risk Assessment and Risk Management (CRARM, 1997) considered that it is wasteful to expend limited risk assessment resources, risk management time and public and legal involvement revisiting the issue of human relevance of the specific response chemical by chemical. The CRARM specifically identified titanium dioxide particles as one such chemical because observed rodent tumour response associated with exposure to TiO2 particles are not relevant to human risk. The Health Effects Institute, also has concluded that rat data should not be used for assessing human lung cancer risk from diesel-exhaust exposure (Health Effects Institute, 1995).

Section 4.1.5, Page 66-69 (Comparison with criteria):

Page 66, 5th paragraph ("No carcinogenic effect was reported…"): the CLH report proposes classification as Carcinogen category 1B via inhalation; in sections 4.1.1.1-4.1.1.4 a large number of studies with other routes of exposure are cited, all of which yield a negative result. ECHA guidance (version 4.1, June 2015) in section 3.6.2.3.2 explicitly states: „Where findings are available from studies using standard routes and non-physiological routes, the former will generally take precedence. Usually studies using non-standard routes provide supporting evidence only. The hazard statement allows for identifying the route of exposure 'if it is conclusively proven that no other routes of exposure cause the hazard' (CLP Annex I, Table 3.6.3).

Further, the CLH report in this paragraph contains an incorrect interpretation of the assumed carcinogenic mode of action, by implying that accumulation of particles may occur in organs other than lungs. In contrast, the only known mechanism is that of particle overload in rat lungs overriding the clearance by macrophages. It is explicitly disputed here that any accumulation in organs occurs via routes of administration other than inhalation (see our detailed comments on toxicokinetics further above); this is consistent with the bulk of scientific evidence clearly documenting that systemic bioavailability of TiO2 is negligible via oral (and dermal) routes. There is no evidence of systemic carcinogenicity whatsoever either in inhalation studies or in any other study.

Page 66, 4th and 6th paragraph states: "category 1B is applicable to substances presumed to have carcinogenic potential for humans, based largely on animal evidence", and "although no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data, lung tumours were reported in 2 inhalation studies in animals, with fine rutile TiO2 (Lee et al., 1985) and nano anatase/rutile P25 TiO2 (Heinrich, 1995), respectively. In the Lee et al (1985) study, (…) increase of bronchioalveolar adenoma was reported in both sexes. In the Heinrich (1995) study, the tumours consisted in bronchioalveolar adenoma, bronchioalveolar adenocarcinoma, cystic keratinizing squamous cell tumours and squamous cell carcinoma. This study is of lower quality since it was performed in females only and with a unique concentration level varying during the experiment. However, since the effects are consistent with those of the other studies, they are considered relevant."

These studies are considered of low reliability and the classification of the tumour types in fact preceded the two international workshops wherein the classifications were re-evaluated by a workshop of expert pathologists. As a result, the Lee et al. (1985) results should be discounted because the high exposure levels clearly exceeded the MTD; even NIOSH in their CIB did not consider them relevant. The Heinrich et al. (1985) study should be rated reliability=3; again, the classification of tumours preceded the re-evaluation of tumour types in the rat. Therefore, a classification should not be based upon these two studies.

Page 66, 6th paragraph states: "Indeed, similar types of lung tumours were reported by Pott & Roller (2005) after intra-tracheal administration of fine anatase TiO2 and nano anatase/rutile P25 TiO2. A further study (Xu et al., 2010) reported a carcinogenic promoter potential (increased multiplicity of lung adenomas and mammary adenocarcinomas) of nano-TiO2 (rutile type, 20 nm) administrated by IPS in transgenic Hras 128 female rats initiated with DHPN."

Both of these studies are not guideline-conform and should be rated as Klimisch reliability 3, and therefore should not be considered for classification. It is well-known that previously the Pott and Roller study has been heavily criticised for the excessively high doses coupled with an inappropriate route of administration, lack of dose response and generally low quality. The Xu et al. study is recognised as inadequate, and does not merit further consideration from the standpoint of supporting a classification.

Page 67, 3rd paragraph states: the CLH report states: "Relevance of these tumours to humans needs to be assessed in order to conclude on the need for classification. First, lung tumours observed after TiO2 inhalation in rats occurred in an overload context, which could suggest that the maximum tolerated dose has been exceeded. Although interspecies variability was found in particle retention, overload concept seems to be relevant for humans (in particular for workers exposed to high dust exposure)..."

This statement is incorrect. Whereas it is true beyond doubt that in rats the MTD was exceeded, there is no scientific evidence whatsoever that the overload concept is relevant for humans – in fact, all available evidence points clearly to the contrary, as discussed above in this comment.

Page 67, 3rd paragraph states: "...since it appears that lung retention and chronic pulmonary inflammation in humans are consistent with the findings in rats".

In contrast to this statement, available data clearly demonstrate that lung retention and chronic inflammation are not consistent with the findings in rats (Nikula et al. 2000). Moreover, the best available evidence suggests that particle disposition and retention and response to particles in monkeys and coal workers have a very different pattern when compared to rats, as also discussed above.

Page 67, 4th paragraph states: "In conclusion, although at this time, the relevance of keratinizing cystic tumour to man remain unclear; other types of tumours (bronchioalveolar adenomas or adenocarcinomas and squamous cell carcinomas) found in rats exposed to TiO2 do occur in humans"

This conclusion is in contradiction to scientific evidence, because humans do not develop lung tumours to PSPs of low cytotoxicity, and the sites at which carcinogenicity due asbestos and cigarette smoke occurs in human lungs are at different locations in the respiratory tract and are of different origin and type. More specifically, the keratinising and cystic tumours are a unique feature in particle overload-exposed rats. (Schulz, 1996; Green, 2000).

Page pages 84-156 (summary of genotoxicity data, also briefly addressed on pages 58-59): The CLH report states that only few studies on bulk titanium dioxide materials are available. However, to reduce the number of references (stated reasoning: "Due to the high number of in vitro genotoxicity assays found, an exhaustive reporting of studies was judged neither feasible nor of any added values"), it was decided during the compilation of the CLH report not to consider all in vitro references published before 2010.

This approach does not comply with the legal requirements as laid down in the CLP regulation (Article 37(1) in conjunction with Annex VI, Part 2 and regulation 1907/2006 Annex I, Section 1-3), whereby:
3. "any relevant information from registration dossiers shall be considered and other available information may be used" (CLP, Annex VI, Part 2)
4. "the evaluation of nonhuman information shall comprise the hazard identification for the effect based on all available nonhuman information" (REACH, Annex I, Section 1.1)

The omission of relevant information merely on the basis of the publication date is clearly not in compliance with the legal requirements. It is further noted that the majority of data relating to the genotoxicity of bulk titanium dioxide was published prior to 2010, and was therefore unrightfully dismissed in the CLH report.

In addition, the studies presented in the genotoxicity annex were not rated according to their relevance, reliability and adequacy (as foreseen in the ECHA guidance Chapter R.4: Evaluation of Available Information, in conjunction with the Guidance on the Preparation of CLH Dossiers, Chapter 5.3). Without such rating, a balanced evaluation of the information against the classification criteria is not possible.

It is important to note that the Nanogenotox (2013) testing programme almost exclusively returned negative findings in genotoxicity tests with a long-lasting testing history, and for which well-established guidelines and procedures are available. In cases where positive findings were received, these were mostly isolated findings in a single cell line and could not be repeated in other cell lines or primary human lymphocytes, and thus should be regarded as not biologically relevant. The overall negative findings in the in vivo systems using three routes of exposure (intratracheal, gavage, intravenous)

corroborates the mostly negative in vitro test results. For test systems investigating the induction of unspecific DNA damage (Comet assay), the in vitro tests largely returned a positive outcome, which were however not biologically relevant or not statistically significant. Similarly, the positive in vivo findings of the comet assay showed serious shortcomings in an inter-laboratory comparison. Considering the overwhelmingly negative tests results in this testing programme, it is concluded that nano-sized titanium dioxide is non-mutagenic, non-clastogenic or non-aneugenic over a wide range of different test systems, which is considered also to apply for bulk-sized (pigment grade) titanium dioxide.

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ECHA note – A confidential and a non confidential attachment were submitted with the comment above.
TDMA-TDIC CLH commentary_Confidential attachment.pdf
TDMA-TDIC CLH commentary_Public attachment.pdf

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM.

Specific response:

- Comments on dermal and oral carcinogenicity are noted. However, this is not an opened point since Anses did not propose a classification for these routes of exposure.
- We also note that TDMA/TDIC declares that titanium dioxide industry does not manufacture any fibrous products. However, fiber-like TiO_2 (nanofibres, nanotubes, nanowires…) has been identified in the literature. In the absence of adequate information in the CSR, these forms are considered relevant for classification proposal.

RAC's response

Noted. RAC concluded that the TiO2 profile of lung carcinogenicity is specifically linked to the inhalation route. Available data with oral and dermal exposure did not result in TiO2 carcinogenicity. The issue of possible fibrous TiO2 has been addressed and discussed in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Switzerland	Karl Bubenhofer AG	BehalfOfAnOrganisation	334
Comment received				
We have been using this substance for decades and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Merck	BehalfOfAnOrganisation	335
Comment received				
The French agency "Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail" (ANSES) elaborated a CLH report with a proposal for a harmonised classification and labelling of titanium dioxide as "potentially carcinogenic to humans" (category 1B) / "may cause cancer by inhalation" (H350i). This classification and labelling proposal is scientifically not justified based on the following reasons: In the given case, the indications of a carcinogenic effect rely exclusively on animal testing in rats. A potential connection between titanium dioxide exposure and lung cancer was examined in several epidemiological studies (case and cohort studies). These epidemiological studies comprises more than 22,000 occupational workers, primarily involved with TiO2 production. These are the potentially most heavily exposed individuals to TiO2 particles. To summarize the findings for all of these studies, no causative link has been demonstrated between TiO2 exposures and cancer incidence (Warheit and Donner, 2015, Food Chem Toxicol, 85, 138-147). This is confirmed in the submitted CLH report for titanium dioxide, which states in chapter 2.2 "Short summary of the scientific justification for the CLH Proposal" that nothing suggests increased cancer risks due to occupational exposure, which is relativized mentioning methodological limitations: "Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable." [CLH Report page 8] No indications of problems for humans are known in practice. We cannot agree that there are relevant methodological limitations. This is also in line with the conclusions from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) in the Technical Report 122 „poorly soluble particles / Lung Overload" (published 01/2014) : "[…] results from several extensive human epidemiology studies in titanium dioxide or				

carbon black exposed workers clearly have demonstrated that long-term occupational exposures to these particle-types do not cause lung cancer or non-cancerous diseases of the respiratory tract."
[ECETOC TR 122, Chapter: Relevance of 'lung overload' for humans].

Two inhalation carcinogenicity studies (Lee et al, 1985; Heinrich, 1995) with rats exposed to titanium dioxide provide the basis for the classification and labelling proposal of ANSES. In this studies, rats chronically exposed to extremely high doses of TiO2 particles in the bulk (Lee et al, 1985) or nano range (Heinrich, 1995) developed lung tumors. The formation of lung tumors in rats after chronic exposure to poorly soluble, nonfibrous particulates of low toxicity have been reported in a variety of studies. However, this finding has not been documented in other mammalian species, including other rodent species (e.g. mice) and larger animals (Warheit & Donner, 2015). The mechanism for tumor development in the rat is thought to occur following high-dose exposures concomitant with long-term studies when particle deposition overwhelms lung clearance mechanisms resulting in a phenomenon called particle overload (ILSI risk science institute workshop, 2000: the relevance of the rat lung response to particle overload for human risk assessment, Inhal. Toxicol., 12, 1-17). This phenomenon is considered rat-specific (Levy, 1995, Indoor environ, 4, 254-262).

For example, in the study from Lee et al., 1985 (see CLH report, Section 4.1.1.2., p. 21-23), particle overload was achieved at the mid dose (50 mg/m3) and the high dose (250 mg/m3). However, only rats exposed to the high dose of 250 mg/m3 ultimately developed pulmonary tumors. The findings of lung tumors at 250 mg/m³ described in the Lee et al. study clearly exceeded the maximum tolerated dose (MTD) and therefore it would be inappropriate to be considered as a positive tumor response. According to the NIOSH Executive Summary of their Current Intelligence bulletin, the 250 mg/m³ concentration in the Lee et al., 1985 study was an excessive dose and is not relevant for human risk assessment (NIOSH Current Intelligence Bulletin 63 – Occupational Exposure to Titanium Dioxide. NIOSH Dept. of Health and Human Services, 2010). In addition, Lee et al. noted that, due to excessive loading in the lungs of rats exposed chronically at 250 mg/m³, the lung tumors were different from common human lung cancers in terms of tumor type, anatomic location, tumorigenesis and were devoid of tumors metastasis. Therefore, the biological relevance of these lung tumors are negligible.
The reliability of the second study, Heinrich (1995) (see CLH report, Section 4.1.1.2., p. 24-26) cannot be evaluated (Klimisch score 3) as only one dose group of female rats and female mice were exposed to titanium dioxide at mean particle mass exposure concentrations varying from 7.2 – 14.8 mg/m3, i.e. a dose response relationship could not be established. Moreover, the evaluation of tumors (including malignant tumors) was assessed and did not consider the 2 international lung pathology workshops – which have reassessed the criteria for describing malignant vs. benign tumors – particularly with reference to the unique cystic keratinizing pulmonary squamous cell lesions which are unique to the rat.

The conclusions from the CLH Report regarding the classification of titanium dioxide are based exclusively on these two studies in rats exposed to extremely high concentrations of titanium dioxide that lead to particle overload effects:
"In experimental animal studies, lung tumours were reported after inhalation or intra-tracheal administration of TiO2 (fine rutile, anatase/rutile P25 nano-TiO2 and nano-rutile) in rats in an overload context. Overload is defined by an impairment of normal pulmonary clearance due to high accumulation of particles. Although inter-species variability was found in particle retention, the overload concept is relevant for humans, and in particular for workers exposed to high dust concentrations." [CLH Report page 8]
By contrast, in chapter 3.9.2.5.3 of the ECHA Guidance Document on CLP the "lung

overload" is expressly mentioned as a mechanism of no relevance for humans, so that it should not be resorted to for classification:
"3.9.2.5.3. Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))
In general, valid data from animal experiments are considered relevant for hu-mans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for hu-mans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans. Examples for such species differences are described in this section.
[…]
Lung Overload
The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate."
[ECHA Guidance document, page 469/470].

Moreover, the following is noted in Guidance document No. 116 of the Organisation for Economic Co-operation and Development (OECD) on the carrying out of carcinogenicity studies:
"3.2.3 The inhalation route of exposure
135. For substances likely to accumulate in the lung over time due to poor solubility or other properties, the degree of lung-overload and delay in clearance needs to be estimated based on adequately designed prestudies; ideally a 90-day study with postexposure periods long enough to encompass at least one elimination half-time. The use of concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged."
There is no doubt that the elimination half-time of titanium dioxide in the animal studies resorted to for classification is in a range which the OECD rejects for the carrying out of inhalation carcinogenicity studies.

A detailed description of the topic "Lung Overload" can be read in the above mentioned ECETOC Technical Report 122 "poorly soluble particles / Lung Overload":
"The synopsis of currently available scientific data on ‚lung overload' allows the Task Force to conclude that
• the rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload.
• lung tumours have to be regarded the final phenotypic `adverse outcome` only in rats, whereas in other species non-neoplastic lesions seem to be the respective `adverse outcome`.
• humans are less sensitive to `lung overload` as epidemiological studies thus far have not been able to detect an association between occupational exposures to poorly soluble particles of low toxicity and an increased risk for lung cancer.
[…]"

Relevance for humans is summed up as follows in the ECETOC Report:
"Therefore, it was noted that the findings in rats are not useful endpoints for human risk evaluations of poorly soluble particulate exposures. In contrast to the experience with rats, epidemiological findings in coal mine workers, a -well studied occupationally-exposed group of workers with routine "particle overload" in their lungs, clearly demonstrate a lack of lung cancer risk when correlated with exposures. In addition, results from several extensive human epidemiology studies in titanium dioxide or carbon black exposed workers clearly have demonstrated that long-term occupational exposures to these particle-types do not cause lung cancer or non-cancerous diseases of the respiratory tract."

[ECETOC TR 122, Chapter: Relevance of 'lung overload' for humans] All relevant guidance documents by ECHA, OECD and the ECETOC report unanimously observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons. As regards inhalation toxicity through insoluble, inert particles, the rat is a particular sensitive species compared with all other studied species: Up until now, evidence of tumours in the respiratory tract has been found only in rats with insoluble, inert particles. Other species – like mouse or hamster – did not develop lung tumours at comparable exposure. Tumour formation in rats is essentially due to particle-induced inflammatory reactions, cell proliferations, secondary genotoxicity through reactive oxygen species and resulting hyperplasia. The above described effects occur particularly in the overload range where particle clearance (clearance/elimination) by alveolar macrophages is massively disturbed. These effects have not been found at all or not to a comparable degree in other species at comparable dose and particle load. For the above expounded reasons, the findings in rats on inhalation toxicity of inert, poorly soluble particles cannot be transferred to humans or are not relevant for humans. Therefore, a classification is neither justified nor appropriate from the toxicological perspective.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		BehalfOfAnOrganisation	336
Comment received				
We have been using this substance for 25 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	J.W. Ostendorf GmbH	BehalfOfAnOrganisation	337
Comment received				
We have no indication within our Company and industry about any carcinogenicrisk of the substance TiO2. It is widely used also in cosmetics and even pharmaceutical industry and has therefore been thoroughly tested without any negative result.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		Individual	338
Comment received				
I am in the paint-industy for 30 years now. TiO2 has allways been used for all white and all light colours as a key material (before, it was lead-white, zink-white). I have never heard of any health problems connected with TiO2.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		Individual	339
Comment received				
We have been using this substance for 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	France	/	BehalfOfAnOrganisation	340
Comment received				
From we use the Tio2 (more than 30 years)we have no cases of cancer in our workforce caused by inhalation of TiO2 during the manufacture of coatings. We are using of efficient ventilation and extraction and personal protective equipment, when handling any material that may be considered a dust hazard. We believe that it is important that this is a generic dust-related statement, rather than specifically related to TiO2 and the classification discussion. The health concern is related to the inhalation of dust yet, due to the hazard-based approach taken by European authorities towards regulating the use of chemical substances, instead of a more pragmatic risk-based approach, all finished liquid products based on TiO2 would be affected by this new classification. TiO2 is a unique pigment that offers opacity, whiteness, UV resistance and compatibility among other advantages. There is no alternative available that matches the performance of TiO2 in our products. We would like at this early stage to alert Authorities to the consequences that a				

classification for TiO2 as a Carcinogen category 1B would cause, one of which being the non-availability of decorative paint to consumers(the consequence of the restriction on the placing of such products on the market according to REACH Annex XVII entry 28). For us it's equal to close a production site, loose certification/homologation and markets at the end.
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	Germany	Jonas Farbenwerke GmbH & Co. KG	BehalfOfAnOrganisation	341
Comment received				
We have been using this substance for 80 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Huntsman Pigments and Additives	BehalfOfAnOrganisation	342
Comment received				
Huntsman fully endorses the scientific data and comments submitted by the TDMA and TDIC on behalf of the industry. The proposed classification is not justified.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Firwood Paints Ltd	BehalfOfAnOrganisation	343
Comment received				
We monitor ill health within our workforce and have no record of any member of staff ever being investigated for cancer which might be attributed to the use and handling of titanium dioxide. All of our staff have regular medical check ups and at no time have the Company Doctors expressed concern over titanium dioxide and other powders handled in				

our factory.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Germany	Steelpaint GmbH	BehalfOfAnOrganisation	344
Comment received				
We have been using this substance for over 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Lithuania	UAB "Veika"	BehalfOfAnOrganisation	345
Comment received				
We fully support the position provided by TDIC ant TDMA, wich is NO labeling/classification of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	A.I.S.E.	BehalfOfAnOrganisation	346
Comment received				
A.I.S.E. supports the scientific position provided by TDMA / TDIC.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	Poland	GEHOLIT POLSKA Sp. z o.o.	BehalfOfAnOrganisation	347
Comment received				
We have been using this substance for as long as our company exists, which is more than 125 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powders at all our workers are protected by local exhaust ventilation or by wearing appropriate dust masks. All controls of the strict German occupational exposure limits in the past years show the reliablibity and ef-fectiveness of these risk mitigation measures. During production all powders are well mixed into and entirely wrapped by binders. After incorporation in our products TiO2 is bound and no longer inhalable. Therefore no specific risks evolve from TiO2 and its specific chemical or physical properties for the users of our products. According to REACH a classification as carcinogen would oblige industry to substitute TiO2 with materials not yet identified, not as well examined, or already banned by industry due to negative properties. There is to date no known alternative in regard to low toxicity or high functionality of TiO2.				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Italy		BehalfOfAnOrganisation	348
Comment received				
It is generally aknowledged that the relevance of animal studies to predict carcinogenicity in humans has severe limitations (Knight, A., Bailey, J. and Balcombe, J, Animal Carcinogenicity Studies: 1. Poor Human Predictivity. 2006 ATLA 34 19-27) ECHA note – A confidential attachment was submitted with the comment above. DECLARATION_(confidential)_2016 TiO2.pdf				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Speciality Coatings (Darwen) Ltd	BehalfOfAnOrganisation	349
Comment received				
We have many years of safe use of Titanium dioxide				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom		Individual	350

Comment received

1. Omission of Ellis et al (2010, 2013) study - The second largest cohort study of TiO2 manufacturing workers has not been included in the CLH report (Ellis et al, 2010: Ellis et al, 2013). This is an update and extension of the Chen and Fayerweather (1988) study which included workers from two TiO2 processing plants. The plants aren't described by Chen and Fayerweather (1988), but Fayerweather et al (1992) notes that one is a large plant on the US east coast (Edgemoor) where all the cancer deaths in the study occurred, and the other is a smaller west coast plant. The study by Ellis et al (2010) included workers from the Edgemoor plant (the data from Chen and Fayerweather [1998] which included workers employed through 1983, were used as the basis for this study with worker data updated from 1983 onward) and two other plants (New Johnsonville and De Lisle). None of the workers were included in the US multicentre study by Fryzek et al (2003). Ellis et al (2010) included over 5000 production workers and 133 lung cancer deaths of which 111 occurred among Edgemoor workers (Chen and Fayerweather et al [1988] reported 9 lung cancer deaths among Edgemoor workers). Lung cancer mortality was less than expected (SMR = 0.90; 95% CI, 0.75-1.05), and no exposure-response relationship was found between TiO2 and mortality from lung cancer and non-malignant respiratory disease. As the CLH report suggests an association between TiO2 exposure and kidney cancer (pages 41 and 48), it is relevant to note that Ellis et al (2010) reported reduced kidney cancer mortality SMR (SMR=0.74; 95% CI, 0.34 to 1.37).

2. CLP regulation (Annex I, section 1.1.1.4) - The dismissal of the strong epidemiological evidence is counter to the CLP regulation (Annex I, section 1.1.1.4), which states that "Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data." The CLH report, and IARC (2010) and NIOSH (2011), provide no strong arguments that the epidemiological studies are not adequate, reliable or representative. However, the regulation also stipulates that "even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data". The epidemiological studies are well conducted, and the findings are robust and replicated in all 3 large cohort studies and 2 large case-control series. Furthermore, statistical power is not a limitation of the epidemiological studies as the 3 key cohort studies (Fryzek et al, 2003; Boffetta et al, 2004; Ellis et al, 2010) include over 24,000 production workers in 18 manufacturing plants in 7 countries, with a total of 457 expected lung cancer deaths of which a high proportion were expected after a sufficient latency period. The Canadian case-control studies included 2093 lung cancer cases (Boffetta et al, 2001; Ramanakumar et al, 2008). In contrast, the animal studies do not paint a consistent picture and the rat studies do not even predict the outcome in mice and hamsters.

3. Study Limitations (section 4.1.2 pages 38-41) - The CLH report dismisses the negative findings of epidemiological studies because "all the studies had methodological limitations; misclassification of exposure could not be ruled out" (page 8). The following limitations of individual studies were listed by the CLH report, but virtually all are minor or irrelevant, and do not limit the ability of the studies to detect an exposure effect:
(i) Boffetta et al (2001) - The CLH report repeats the comment made by IARC (2010) that the main limitations of the study are "the reliance on self-reported occupational histories and expert opinion rather than measurement of exposure". The authors clearly couldn't think of any major limitations as the exposure assessment approach is an excellent example of good epidemiological practice. The investigators were able to accurately identify subjects exposed to TiO2, well characterise "nonsubstantial" and "substantial" exposure, and relate exposure levels to those in the TiO2 manufacturing industry. The CLH report also restates additional limitations listed by the NIOSH (2011). These include the use of surrogate indices for exposure which wrongly suggests that the investigators used a simple surrogate of exposure such as job title when in fact exposure was assessed by a team of industrial hygienists using a detailed occupational questionnaire and available industrial hygiene data from various industries. Another so-called limitation relates to the small numbers of subjects exposed to welding fumes containing TiO2, but this has no relevance to the main conclusion of the study. It is true that particle sizes were not characterised, but this is clearly impractical in a case-control study and the study only makes inferences about exposure to TiO2.
(ii) Ramanakumar et al (2008) – The CLH report only states that the limitations are the same as those of Boffetta et al (2001), and hence minor.
(iii) Chen and Fayerweather (1988) – This study is now less relevant following the update by Ellis et al (2010, 2013). However, the criticism of it by the CLH report shows a clear lack of balance. Cancer incidence analyses are criticised because "incident cases of cancer only in actively employed persons were used for both observed and company reference rates" (page 40), but the CLH summary gives no results from mortality analyses, including the statistically significant reduction in lung cancer mortality compared to US rates (SMR, 0.52; 95% CI, 0.24–0.99). Mortality analyses also included pensioners and non-pensioned terminated employees, and consequently had much less potential for bias. It is also stated that details of exposure to TiO2 and other factors were not described, but this is not correct as the investigators reported details of estimated cumulative exposure to TiO2 and described other chemicals that might have confounding effects, and how jobs were assessed for exposure to these chemicals. The CLH report also notes that cancer mortality and specific cancer sites were not reported in detail, but this is a minor limitation as the focus of the study was respiratory/lung cancer. Finally, the CLH report reiterates the naïve criticism of the study made by NIOSH (2011) stating that "It has also been noted that the presence of other chemicals and asbestos could have acted as confounders" (page 40). This would have increased lung cancer mortality in the cohort unless it is being suggested that TiO2 workers are less likely to be exposed to other chemicals and asbestos than the general public?
(iv) Fryzek et al (2003) – The study is criticised because "the cohort was relatively young (about half were born after 1940) making the duration of exposure to TiO2 and the latency period for the development of lung cancer rather short". In fact, far more than half were born after 1940 (71%), but that does not mean that the follow up period was too short to determine an exposure effect. Fryzek et al (2003) did not report how many lung cancer deaths were expected more than 20 years after the start of exposure, but the lung cancer analysis for this follow-up time period (SMR, 1.1; 95% CI, 0.8-1.5) gave almost identical results as the overall analysis (SMR, 1.0; 95% CI, 0.8-1.3), and hence indicates that the study had sufficient latency to detect an exposure effect. The CLH report also stated that the oldest company reports were not available for the investigators to evaluate, but in fact the investigators stated that it is possible that some company

records from the early periods in the plants may have been destroyed or lost, but we found no evidence to support such an assumption. The other limitations listed include limited data on non-occupational factors (e.g. smoking) and lack of information about ultrafine exposure. The lack of smoking data is a limitation when making external comparisons with US mortality rates, but far less so in internal analyses which showed that relative risks for lung cancer and non-malignant disease decreased with cumulative exposure. The studies do lack information about ultrafine exposure, although it is well recognised that pigmentary TiO2 has an ultrafine tail.
(v) Boffetta et al (2004) - The limitations listed by the CLH report are those given by IARC (2010) and include lack of adjustment for smoking, but it is noted that the availability of data on tobacco smoking for slightly more than one-third of the cohort, provided some reassurance that tobacco smoking was unlikely to be a confounder. Another limitation is stated to be possible exposure misclassification, although it is also stated that IARC (2010) listed the detailed exposure assessment as one of the strengths of the study. It is also stated that the exclusion of part of the early experience of the cohort from the analysis, reduces the power of the study to detect an association. The investigators raised the possibility of survival bias resulting from this, but concluded that the results of additional analyses argue against it. A final limitation is "the relatively recent beginning of operation of some of the factories that resulted in a follow-up period that was too short to allow the detection of an increase in risk for lung cancer" (page 41). This is clearly isn't the case as Table 5 of Boffetta et al (2004) shows that 88.0 lung cancer deaths were expected during the period 20 to 30 years after start of employment, and a further 93.9 lung cancer deaths were expected 30+ years after start of employment (~ ¾ of all the expected lung cancer deaths). There was clearly adequate power to detect even a small increase in lung cancer.

4. Misclassification of exposure (section 4.1.2, pages 38-41) - There is also no reason to believe that misclassification of exposure seriously undermined the ability of the epidemiological studies to detect an exposure effect. Possible exposure misclassification is only listed as a limitation of Boffetta et al (2004) by the CLH report (page 41), and no explanation is given why it should be seen as a particular limitation of this study. An extremely comprehensive exposure assessment was performed for this study which the CLH report appears to acknowledge (citing IARC [2010]) when it describes the "detailed exposure assessment" as one of the strengths of the study (page 41).

5. Imbalanced/inaccurate summaries of studies (section 4.1.2, pages 38-41) - The epidemiology study summaries contain numerous inaccuracies and instances where negative findings are omitted or downplayed, while emphasising weak evidence of a possible exposure effect:
(i) Boffetta et al (2001) – The CLH report doesn't mention that Boffetta et al (2001) is a more in depth analysis of the association between TiO2 exposure and lung cancer in the study by Siemiatycki (1991) and included the same cases, a subsample of controls, and an improved exposure assessment.
(ii) Ramanakumar et al (2008) – It is incorrect to state that "some results from the first study have already been described in the publication Boffetta (2001)". Boffetta et al (2001) used a more refined exposure assessment methodology and identified different numbers of cases with any or substantial exposure to TiO2. The numbers of cases with any or substantial exposure to TiO2 agree with Siemiatycki (1991), but the results are different. Unfortunately, the CLH report does not list any study results from Ramanakumar et al (2008), including the ORs for the 3 TiO2 exposure categories from the pooled analysis which provide an obvious summary. Instead it is noted that "some odd ratios of lung cancers were above 1.0", but "none were statistically significantly increased" (page 39). This wording is not only uninformative, but it might be wrongly interpreted as indicating an exposure effect that the study had insufficient power to

detect.
(iii) Siemiatycki (1991) - It is noted that an "indication of excess risk" was found in relation to squamous-cell lung cancer (OR 1.6; 90% CI, 0.9–3.0; 20 cases), but the CLH report doesn't mention that Boffetta et al (2001) did not confirm the finding for squamous cell carcinoma in a more in depth analysis using an improved exposure assessment (OR 1.1; 95% CI, 0.6–2.0; 16 cases).
(iv) Fryzek et al (2003) - The CLH report provides no information about the findings of internal dose response analyses which IARC (2010) noted "showed that relative risks for mortality from all causes and mortality due to lung cancer and non-malignant respiratory disease decreased with increasing cumulative exposure". However, the CLH summary notes that new internal analyses made in response to criticisms made by Beaumont et al (2004) yielded hazard ratios similar to those in the original analysis. This statement is meaningless when no information is provided about the original analysis. It is not correct that "SMRs for mortality …. due to lung cancer and non-malignant respiratory disease decreased with longer durations of employment" (page 40) as there is no such trend for non-malignant disease: the study investigators actually stated that "No trends of increasing SMRs for malignant and nonmalignant lung disease with increasing duration of employment were evident". The summary of the sampling data for Fryzek et al (2003) is also uninformative as it does not state what was measured (total TiO2 dust), how it was sampled (personal samples), or what geometric means were calculated (those for 5-year time intervals).
(v) Boffetta et al (2004) – No numbers of observed and expected lung cancer deaths are given. It is also not mentioned that the investigators believed "that the statistically significant 23% increase in lung cancer mortality detected in the SMR analysis may be explained by a combination of factors other than TiO2 dust exposure," including the important observation that 8 of the 10 regions where the factories were located had a higher death rate from lung cancer than the national rate for their country, which implied that the SMR for lung cancer would have been lower if regional reference mortality rates had been used. Instead, the CLH report gives considerable space to discussing a "suggested" dose-response relationship between exposure to TiO2 and mortality from kidney cancer which was not even statistically significant (pages 41 and 48). This was dismissed by the study investigators because the lack of an overall increase in the SMR of kidney cancer "suggests that this trend observed was due to a reduced mortality among workers in the lowest category of estimated cumulative exposure," and the CLH report notes that other cohorts did not report an increased risk of kidney cancer. In fact, Boffetta et al (2004) also reported reduced kidney cancer mortality (SMR = 0.82; 95% CI, 0.51-1.29). Finally, there was no relationship between lung cancer and cumulative exposure to TiO2, not "there was no relationship with exposure to TiO2 considering … concentration" as stated on page 41.

6. Section 4.1.4 Inhalation route – human data (p 48-50) – It is stated that "no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data" (page 50) but this conclusion is based on a very selective summary of the findings of the epidemiology studies:
(i) Firstly, the CLH report claims (page 48) that a significantly elevated risk for lung cancer was observed in two of the three cohort studies. However, Fryzek et al (2003) did not observe an elevated risk for lung cancer mortality overall, but an "elevated SMR was found in short-term workers (≤ 9 years) after 20 or more years of follow-up". The CLH report states that "it decreased with longer duration of employment". In fact, reduced lung cancer mortality was reported among longer duration workers during the same period of follow-up, and there was no other evidence of an association between TiO2 exposure and lung cancer. The summary of this study by IARC (2010) did not even mention the finding for short-term workers. This may be because there are well-recognised differences between short-term workers and long-term workers in lifestyle and

other factors that are much more likely to explain the elevated SMR in short-term workers than TiO2 exposure. Bugge et al (2010) notes that many studies have addressed the fact that cancer incidence, especially lung and other lifestyle-associated cancers, is often increased among short-term workers, and that many occupational epidemiological studies show increased cancer risk in this group only. Boffetta et al (2004) did report significantly elevated lung cancer mortality overall, but considered that this may be explained by a combination of factors other than TiO2 dust exposure, and concluded that the results of the study "do not suggest a carcinogenic effect of TiO2 dust on the human lung".
(ii) The non-significant kidney cancer trend observed by Boffetta et al (2004) is again noted, even though there is no other evidence from this study, or others, to support the conclusion that "a dose-response relationship was suggested".
(iii) It is again stated that that methodological limitations were noted for all studies, but the CLH report has not demonstrated that the human data are not adequate, reliable or representative.
(iv) It is also noted that primary particle size or size distribution of the TiO2 particles are lacking and that in this context, epidemiological data are considered inadequate. As noted earlier, the epidemiological studies do lack information about ultrafine exposure, but it is well recognised that pigmentary TiO2 has an ultrafine tail. Hence, the conclusions of the epidemiological studies apply to both nano and pigmentary TiO2.

References

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Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	West and Senior Limited (WSL)	BehalfOfAnOrganisation	351
Comment received				
We question the validity of re-classification based upon the limited and questionable laboratory data versus the extensive safe use in industrial application. We question if the perceived hazard reflects or is proportionate to the reality of low and well managed risk. Please see attached document. ECHA note – A non confidential attachment was submitted with the comment above. Titanium Dioxide Response to Public Consultation WSL.pdf				
Dossier Submitter's Response				
See point 4 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	PlasticsEurope Deutschland e.V.	BehalfOfAnOrganisation	352
Comment received				
The conclusions from the CLH Report regarding the classification of titanium dioxide are based exclusively on studies in rats exposed to extremely high concentrations of titanium dioxide that lead to so-called "lung overload" effects [CLH Report page 8].				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Switzerland	Novartis	BehalfOfAnOrganisation	353
Comment received				

Mode Of Carcinogenic Action
NIOSH concluded that TiO2 is not a direct-acting carcinogen, but acts through a secondary genotoxicity mechanism that is not specific to TiO2 but primarily related to particle size and surface area (NIOSH, 2011).
Particle-induced pulmonary inflammation, oxidative stress, lung tissue damage, and epithelial cell proliferation are considered to be the key steps leading to lung tumor development in the rat acting through a secondary genotoxic mechanism. Oxidative stress is considered the underlying mechanism of the proliferative and genotoxic responses to poorly soluble particles including TiO2 and other poorly soluble, low toxicity substances (PSLT).
Fine and ultrafine TiO2, like other PSLT, can elicit persistent pulmonary inflammation at sufficiently high dose and/or duration of exposure. This occurs at doses that impair the normal clearance of particles from the alveolar (gas exchange) region of the lungs, i.e., "overloading" of alveolar macrophage-mediated particle clearance from the lungs.
In rats, a mean airborne concentration of 3 mg/m3 fine-sized TiO2 was estimated as the No Observed Adverse Effect LevelOAEL, which was defined as a 95% probability that the lung responses would be below those predicted using the "no overload level" for the average animal. This implicates that pulmonary inflammation causing oxidative stress, ultimately leading to tumour formation would occur only at high dose levels, which is confirmed by all rat inhalation carcinogenicity studies performed (NIOSH, 2011).

Non-Clinical Carcinogenicity Studies and Their Relevance for Occupational Exposure
Carcinogenicity was studied in rodents (mouse, rat, hamster) for the following routes of administration: oral, inhalation, intratracheal, subcutaneous and intraperitoneal. In all studies, but inhalation and intratracheal administration in rats, no difference in the incidence of tumours was observed between treated and control animals.
Relevant studies and results are described below (IARC, 2010):
Inhalation studies:
- A study in mice exposed to ultra-fine TiO2 (for 18 hour per day on 5 days per week for up to 13.5 months (7.2 mg/m3 for the first 4 months, then 14.8 mg/m3 for 4 months and 9.4 mg/m3 for 5.5 months) showed that the lung tumour rate in mice was not significantly influenced by exposure to TiO2.
- A study in rats exposed to ultrafine TiO2 at an average of approximately 10 mg/m3, 18 h/day 5d/wk, for up to 24 months (7.2 mg/m3 for 4 months, followed by 14.8 mg/m3 for 4 months, and 9.4 mg/m3 for 16 months). Following 6 months without TiO2 exposure. At 6 months of exposure, 99/100 of the rats had developed bronchioloalveolar hyperplasia, and by 2 years all rats had developed slight to moderate interstitial fibrosis. After 24 months of exposure, four of the nine rats examined had developed tumors (squamous cell carcinomas, adenocarcinoma, and benign squamous cell tumors). At 30 months (6 months after the end of exposure), a statistically significant increase in adenocarcinomas was observed (13 adenocarcinomas, in addition to 3 squamous cell carcinomas and 4 adenomas, in 100 rats). In addition, 20 rats had benign keratinizing cystic squamous-cell tumors.
- In a study in rats exposed to 0, 10, 50 or 250 mg/m3 (rutile; 99% pure; mean diameter 1.5–1.7 μm) for 6 hour per day on 5 days per week for 2 years, no differences in mortality, body weights or clinical signs were observed. The incidence of lung tumours was increased in both male and female high-dose rats. The tumours found (lung adenomas) were benign, and approximately half of them were later re-classified as transitional cell carcinomas and keratinizing squamous cell tumours.

- In rats exposed for 2 years by inhalation to 10 mg/m3 of ultra-fine TiO2, or diesel engine exhaust (7 mg/m3), or carbon black (11.6 mg/m3) lung tumor rates increased with increasing cumulative particle exposure (mg/m3 x h) independent of the type of particle employed. Mice that were kept in the same exposure atmospheres (high diesel soot, carbon black, TiO2) as the rats, did not show an increased lung tumor rate.

Intratracheal:
- In a study in rats, animals were administered different types of ultrafine TiO2 by intratracheal instillation (see table). Statistically significant increases in benign and/or malignant lung tumours were observed with both types of hydrophilic titanium dioxide.
- The ANSES (2016) report states the following:
- In experimental animal studies, lung tumours were reported after inhalation or intra-tracheal administration of TiO2 (fine rutile, anatase/rutile P25 nano-TiO2 and nano-rutile) in rats in an overload context. Overload is defined by an impairment of normal pulmonary clearance due to high accumulation of particles. Although inter-species variability was found in particle retention, the overload concept is relevant for humans, and in particular for workers exposed to high dust concentrations (ANSES, 2016).
-
- In the ECHA Classification and Labelling Guidance Document (ECHA,2008) the "Lung overload" is explicitly mentioned in the section 3.9.2.5.3. as a mechanism that is unlikely to be relevant to humans and therefore should not be used for classification as follows:
-
- "3.9.2.5.3. Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))
- In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans. Examples for such species differences are described in this section.
- […]
- Lung Overload
- The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate.
-
Human Carcinogenicity Studies and Their Relevance for Occupational Exposure
IARC discussed three epidemiological studies looking at cancer mortality of workers in the TiO2 industry. The studies performed by Chen & Fayerweather, 1988 and Bofetta et al, 2004 were considered to have some methodological limitations compared to the study by Fryzek et al, 2003. None of the studies found a relationship between exposure to TiO2 and number of cancer cases or standardized mortality ratio (IARC, 2010).
ECETOC technical report no. 122 (2013) describes that there was no indication of a positive association between occupational exposure and death from all causes, all cancers, lung cancer, non-malignant respiratory disease, or all heart disease in a cohort study of 3'607 workers employed in three DuPont TiO2 production facilities, which were followed with the exposure assessment by industrial hygienists from 1935-2006 (ECETOC, 2013).
The ANSES (2016) report indicates the following:
Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable.
Although the full mode of action is still unclear, an inflammatory process and indirect genotoxic effect through Reactive Oxygen Species (ROS) production seems to be the major mechanism to explain the effects induced by TiO2. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO2 particles.

The relevance of the poorly soluble particles and lung overload for human carcinogenicity was described by ECETOC in their Technical Report 122 (ECETOC, 2013). They have concluded as follows:
As noted in the ILSI Workshop Report 2000, high-dose, long term exposure to poorly soluble particulates (PSPs), which produce lung tumors in rats, do not induce neoplastic pulmonary effects in similarly exposed mice and hamsters. Moreover, the abundance of available clinical and epidemiological data in occupationally-exposed workers is consistently negative for lung cancer as well as non-neoplastic lung diseases. Levy (1995) concluded that the findings of rat specific lung neoplastic responses to chronic PSP exposure are unique to that species. Therefore, it was noted that the findings in rats are not useful endpoints for human risk evaluations of poorly soluble particulate exposures. In contrast to the experience with rats, epidemiological findings in coal mine workers, a -well studied occupationally- exposed group of workers with routine "particle overload" in their lungs, clearly demonstrate a lack of lung cancer risk when correlated with exposures. In addition, results from several extensive human epidemiology studies in titanium dioxide or carbon black exposed workers clearly have demonstrated that long-term occupational exposures to these particle-types do not cause lung cancer or non-cancerous diseases of the respiratory tract (ECETOC, 2013).

Human Exposure Routes Relevant for Possible Development of Cancer
TiO2 has been classified in humans and animals as biologically inert (Ophus et al., 1979; Lindenschmidt et al., 1990).

Skin exposure
The skin of an adult person is, in most places, covered with a relatively thick (~10 µm) barrier of keratinised dead cells. TiO2 and zinc oxide (ZnO) particles are used in sunscreens to avoid the harmful effects of ultraviolet radiation in sunlight to physically reflect (i.e., scatter) the ultraviolet radiation or trap the ultraviolet photon in the crystal matrix. One of the critical questions regarding the safety of a topically applied material is whether the material will penetrate the epidermal barrier of the skin or follicular lumen and distribute to the dermis and other organs. Penetration of TiO2 is not expected for non-micronized particles. To assess the penetration of the ultra-fine TiO2, Sadrieh et al. (2010) performed a 4-week dermal exposure to three different TiO2 particles (uncoated submicron-sized, uncoated nano-sized and coated nano-sized) in 5 % sunscreen formulation with minipigs. They have concluded that the findings indicate there is no significant penetration of TiO2 nanoparticles through the intact normal epidermis. Therefore, risk of TiO2 with topical applications is negligible since TiO2 does not penetrate the skin.

Oral exposure
Titanium dioxide (E 171, INS 171) is approved for use in food by the European Union, by the United States FDA and by the Codex Alimentarius of the FAO/WHO. The Joint WHO/FAO Expert Committee of Food Additives (JECFA) evaluated titanium dioxide and allocated an Acceptable Daily Intake (ADI) not specified (JECFA 1969). In addition to the safety evaluation, JECFA established a set of purity criteria for titanium dioxide which do not differentiate between the anatase and rutile forms of titanium dioxide. In the European Union, titanium dioxide (E171) is included in the list of approved colouring agents in Directive 94/36/EC. The purity criteria, however, mention explicitly that titanium dioxide essentially consists of the pure anatase form, which may be coated with small amounts of alumina and/or silica to improve the technological properties of this product.
Rutile titanium dioxide, platelet form is currently used in aqueous film coating systems for commercial confectionery products in the United States. Rutile titanium dioxide, platelet form is permitted for food and drug use in the United States (under 21 CFR § 73.575 and

the Inactive Ingredient Database). According to 21CFR73.575 bullet point (c) Uses and restrictions the color additive titanium dioxide may be safely used for coloring foods with the restriction that the quantity of titanium dioxide should not exceed 1 percent by weight of the food. Rutile titanium dioxide, platelet form is being evaluated for the use in cookies, pretzels, baked goods, salted snacks, and confectionery products in the United States.
JECFA evaluated the safety of titanium dioxide including studies on absorption, distribution, metabolism, excretion, acute, short-term and long-term toxicity. JECFA concluded that: "Titanium dioxide is a very insoluble compound. The studies in several species, including man, show neither significant absorption nor tissue storage following ingestion of titanium dioxide. Studies on soluble titanium compound have therefore not been reviewed. It is useful to note that following absorption of small amounts of titanium ions no toxic effects were observed (EFSA, 2004). Therefore, risk of TiO2 with oral applications is negligible and there is no evidence of carcinogenic effect with oral exposure.

Inhalation exposure
The relevant route of TiO2 exposure for carcinogenic effects is only the inhalation exposure to titanium dioxide dust. The effect is, based on the current understanding, primarily to particle-based inflammatory processes in the lungs, which can subsequently lead to the formation of tumors, and is not substance-specific. If titanium dioxide for example is in the form of a suspension, the particle-based inflammatory effects do not materialize.
An inhalation exposure to titanium dioxide dust can be expected primarily at workplaces. Workplace limit values for various fractions of TiO2 or inert dust from several countries and organisations can be found in the table (see full pdf report).

Conclusions
There is no known risk for carcinogenicity of TiO2 of any modification and size with dermal or oral exposure. TiO2 is safely used in cosmetics, as food additive and as pigment for pharmaceutical products. Also for the inhalation route of exposure the evidence of TiO2 being carcinogenic to humans is very limited. Multiple epidemiological studies do not show any relationship between exposure and cancer incidence and in the animal studies an increase in tumors was found in rats only and at very high doses, causing 'lung overload'. Lung overload most reasonably can be considered a species specific effect.
In Novartis, occupational risks to chemicals due to exposure are managed in accordance with their corporate guidelines. The Determination of an Occupational Exposure Limit (OEL) For Drug Substances and Intermediates standard defines the procedure for Novartis Pharma to calculate the OEL. The occupational exposure to raw materials, such as TiO2, is limited by applying country specific regulatory limits when applicable and internationally recognized limits such as MAK, TLV, PEL or similar values in the absence of country specific limits.
GHS classification has to be based on substance-specific properties and the weight of evidence needs to consider human experience on occupational health data where appropriate. General lung overload in animal experiments with substances which cannot be degraded by the body is not a substance specific property and is contradicted by results from human epidemiological studies.
Therefore we consider assigning a hazard classification of category 1B ("presumed to have carcinogenic potential for humans") / H350i 'may cause cancer by inhalation' for TiO2 not being applicable. The proposed change in classification and labelling would not contribute to the protection of workers.

References
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ECHA note – A non confidential attachment was submitted with the comment above. NVS final.pdf

Dossier Submitter's Response

See points 1 ,2 and 4 of the attachment to the RCOM.

For specific point in the attachment linked to skin and oral exposure, no carcinogenic potential is expected for titanium dioxide as assessed in the CLH report.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	IMA-Europe	BehalfOfAnOrganisation	354

Comment received

IMA-Europe supports the specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA) and the Titaniun Dioxide Inductry Consortium (TDIC).

Dossier Submitter's Response

See response to TDMA/TDIC comment No. 99.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	ALBIS Plastic GMBH	BehalfOfAnOrganisation	355
Comment received				
We follow the arguments given by Prof. dr. dr. Uwe Heinrich, the author of the study "(Heinrich et al (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide)" and the MedPharmPlast Europe, a sector group of the European Plastics Converters, that: • Rats are uniquely susceptible to "lung overload" • If a toxic effect exists it is due to the particle not the substance itself. In his opinion an OEL for dust, respirable dust and ultrafine dust (<100nm) would be a better solution to cover the risks associated with this particular issue. As CLP legislation is a substance specific policy instrument, it would not be appropriate to classify the entire substance based on an effect seen with particle of all low solubility substances.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Kestrel Building Products	BehalfOfAnOrganisation	356
Comment received				
Kestrel Building Products supports the scientific position of the TDMA and opppose the French proposal to change the classification of Titanium Dioxide. ECHA note – A confidential attachment was submitted with the comment above. Kestrel Building Products - Classification Proposal for Titanium Dioxide.docx				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany	Paul Jaeger GmbH & Co KG	BehalfOfAnOrganisation	357
Comment received				
In our long company's history we never had any cases of sickness that were related to the use of titanium dioxide. Neither have we heard about such cases. Titanium dioxide is known to be inert. As we all know it is necessary to have a protection against any type of dust during the work with powders in order to avoid respiration. This is generally done in our company. Limits of dust in the air are the only way to assure the worker's safety. Respirating any kind of dust / powder in high concentrations is a serious health risk.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Swish Building Products	BehalfOfAnOrganisation	358
Comment received				
Swish Building Products supports the scientific position of the TDMA and oppose the French proposal to change the classification of Titanium Dioxide ECHA note – A confidential attachment was submitted with the comment above. Swish Building Products Oppose the French Classification Proposal for Titanium Dioxide.docx				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		BehalfOfAnOrganisation	359
Comment received				
Besides single animal testing studies, which do not show an increased cancer risk by inhalation of TiO2 particles, the CLH report also mentions quite a number of animal tests (mainly on rats), that indicate increased tumor formation after inhalative or intratracheal application of TiO2 in the overload context. However, the actual relevance of these positive results for humans is questionable: Hext et al. for example proved clear differences regarding the clearance rate from the lung of rats, mice and hamsters, depending on the animal species. This can lead to variable sensitivity towards the inhaled particles [1]. Studies on other insoluble particles show that, in the lungs of coal miners, particles can indeed be accumulated. However, this does not necessarily exert inflammatory reactions and the resulting formation of lung tumors as in the case of animal studies on rats [2]. Also the exposure of rats and monkeys with diesel exhaust dust caused hyperplasia and inflammatory reactions of the alveolar epithelium only in the rat [3]. From the authors` point of view one possible reason could be that in case of the rat particles mainly accumulate in the lumen of the alveolar ducts and the alveolus, whereas in monkeys the accumulation takes place in the interstitium. The authors conclude that the findings gained on rats cannot necessarily be transferred to monkeys. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) comes to a similar conclusion in their technical report „Poorly Soluble Particles / Lung Overload" [4]. They highlight that rats react much more sensitive to the inhalation of insoluble particles than humans, primates or other rodents. Under the same conditions, tumor formation appears especially in rats but not in other animal species. This fact is traced back to the considerable impact on the lung clearance mechanisms, resulting in a particle overload in the lung of rats at high exposure. This, in turn, affects the alveolar macrophages, mainly responsible for particle removal from the alveolus. Inflammation reactions of the lung and pathological changes follow pulmonary fibrosis or even the formation of lung tumors may result. However, these tumors are specific for rats. Other authors also emphasize that				

studies, resulting in a lung overload in rats, are no reliable source for concluding a potential cancer capability in humans [5-7].
On the one hand, the used inhalation doses exceed by far the concentrations expected in case of lifetime exposition of workers. On the other hand, the observed pathological tissue changes in rats by persistent lung overload are not particle-specific, but specific for the species rat and are not valid for other species. Even the guidance document on the application of the CLP criteria of ECHA questions under item 3.9.2.5.3. (Mechanisms not relevant to humans) the criterion lung overload with regard to a direct transfer of animal study results on humans [8].
The epidemiological studies on workers of TiO2 production from 11 European and 5 US locations summarized by the IARC monograph and by Hext et al. examined a possible increased incidence of lung cancer after long-term TiO2 exposure [9-15]. The results of the studies do not indicate any carcinogenic effect of TiO2 dust on the lungs. Accordingly, the data strengthen the presumption that the existing animal testing data do not allow a causal conclusion to the application in humans.

Final conclusion
On the basis of the available data, in particular the extensive epidemiological observations, the proposed classification of TiO2 as Carcinogen 1B – H350i ("May cause cancer by inhalation") is neither scientifically proven nor comprehensible. The usage of TiO2 in various industrial sectors and a wide number of consumer products for decades does not indicate any risk that justifies a respective classification.

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risk of lung cancer in a population-based study from Montreal. Scand. J. Work Environ. Health 27, 227–232.
13. Siemiatiycki, J. et. (1991). Risk Factors for Cancer in the Workplace, CRC Press, Boca Raton, FL.
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15. Ramanakumar, A.V., Parent, M.E., Latreille, B., et al. (2008) Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: results from two case-control studies in Montreal. Int. J. Cancer 122, 183-189.

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany		BehalfOfAnOrganisation	360
Comment received				
We have been using this substance for 92 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Austria		BehalfOfAnOrganisation	361
Comment received				
As a conclusion no cancer to humans is observed caused by TIO2 therefore we follow the statement of TDIC and TDMA for none labelling of TIO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	MedPharmPlast Europe	BehalfOfAnOrganisation	362
Comment received				
See MedPharmPlast Europe Position Paper. ECHA note – A non confidential attachment was submitted with the comment above.				

MPPE Position Paper - Classification of TiO2.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Japan	KANEBO cosmetics INC.	BehalfOfAnOrganisation	363

Comment received

We believe TiO2 does not have carcinogenic potential on humans from following reasons.
Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ.
The causal relation of the carcinogenicity associated with titanium dioxide has not been reported since titanium dioxide has placed in the market for more than 90 years.
In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.
According to two inhalation studies in rat, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumours, and adenocarcinoma were observed only in female rats, whilst it was not recognized that the increase of carcinogenesis or the increase of mortality in other two studies in rats or a study in mice. In addition, two inhalation studies in rat mentioned above, the study exposed rats to titanium dioxide at concentrations of 0, 10, 50, 250 mg/m3 showed that the maximum dosage caused bronchioalveolar adenoma, and it suggested overloading context (Lee, 1985 R2). It's known that pulmonary responses to inhaled particles of TiO2 differ by species, we consider that it's inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans.

We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses.

We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.

Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM. Please note that data were considered sufficient for the classification proposal for carcinogenicity.
RAC's response
Noted. RAC thoroughly discussed the reliability of data for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	KEIMFARBEN GmbH	BehalfOfAnOrganisation	364
Comment received				
We have been using this substance for 138 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect themselves from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled in its pure form, as powder.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Belgium		BehalfOfAnOrganisation	365
Comment received				
We do support the scientific position provided by TDMA/TDIC				
Dossier Submitter's Response				
See response to TDIC/TDMA comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Greece		BehalfOfAnOrganisation	366
Comment received				
We fully support the position provided by TDIC and TDMA which is no labelling of Tio2				
Dossier Submitter's Response				
See response to TDIC/TDMA comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	United Kingdom		Individual	367
Comment received				
Human data does not suggest an association between occupational exposure to TiO2 and risk for cancer. (CLH report page 8) The exposure levels required are not clear and as far as reported no real life incidents in workers have been established as facts. In this case with such overwhelming evidence of safe use the classification is clearly not sound and should not be applied. In a product with such overwhelming evidence of safe use even in				

prolonged direct skin contact and inhalation during removal phases of paint and other coating plastics there can be no justification for such a risk classification. This appears to be confirmed by the findings on pages 20 through 23 of the CLH report and again on p39 "Cohort analysis suggested that the risks of developing lung cancer and other fatal respiratory diseases were not higher for TiO2-exposed employees than for the referent groups. Nested case-control analysis found no statistically significant associations between TiO2 exposure and risk of lung cancer, chronic respiratory disease and chest roentgenogram (X-ray) abnormalities." and on p 50 the conclusion is actually much clearer than the report suggests when it says "...no definitive conclusion can be drawn about the carcinogenic effect after inhalation of TiO2 based on human data" and hence the groups findings on p66 are at best speculative and at worst erroneous, drawing too much from statistically insignificant findings when compared with real life available data. Based on the above there can be no justification whatsoever for classifying titanium dioxide as a potential carcinogen. Real life data in fact shows the opposite as reported in the CLH report and it is surprising to see such conclusions drawn.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		BehalfOfAnOrganisation	368
Comment received				
TiO2 is tightly incorporated into the rubber matrix of our products, hence there is no inhalation exposure to the customer. Regarding the chemical exposure of our employees handling TiO2: we handle TiO2 under forced ventilation (air extraction) and we monitor the exposure against the general exposure limits as defined in the TLV (MAK) <1,25mg/m3 of respirable dust and <10mg/m3 of inhalable dust. We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See points 1 and 4 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	Germany	Eternit GmbH	BehalfOfAnOrganisation	369
Comment received				
No special case of cancer related to Titanium dioxide is observed during the last 50 years.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	BASF Coatings GmbH	BehalfOfAnOrganisation	370
Comment received				
As for other solids, workers inhalative exposure to dust is controlled and risk reductions measures are in place. The general dust limit values (TRGS 900 in Germany, similar limit values in other countries) are observed. Although Titanium dioxide has been used for many decades, no increased worker's incidence of lung cancer has been observed.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Marabu GmbH & Co. KG	BehalfOfAnOrganisation	371
Comment received				
I believe that a classification as Carc. Cat. 1B is disproportionate, as we have been using this substance for at least 50 years, and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers during this time. I am not a toxicologist, however the comments outlined in the TDMA/TDCIcommentary on the CLH report to my opinion are convincing reasons for not classifying TiO2 as a carcinogen.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Landshuter Lackfabrik	BehalfOfAnOrganisation	372
Comment received				
We have been using this substance for more than 70 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Siegwerk	BehalfOfAnOrganisation	373
Comment received				
TiO2 is a key material to manufacture our products. It is by far the most important white pigment for the printing ink industry and there is no suitable alternative available. We have been using now this substance for many decades in the manufacture of printing inks. When handling titanium dioxide or when handling any other material that may be considered a dust hazard appropriate risk management measures like local exhaust ventilation (LEV) are in place at every of our sites in order to comply with already existing relevant thresholds. In addition to the technical precautions, our workers use suitable safety equipment (e.g. dust masks) to protect them properly from dusty materials. We are not aware of any relation between the use of TiO2 and the development of cancer by our workers. Neither do we have any evidence for that nor have we ever been approached with that suspicion. Although the classification proposal is for TiO2 as inhalable dust, it would also massively affect liquid and pasty products like printing inks, even though it is not available for exposure by inhalation from our products. This is the result of the hazard-based approach for classification and labelling of current EU chemicals legislation instead of a risk-based approach.				
Dossier Submitter's Response				
See points 1, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Gleitsmann Security Inks GmbH	BehalfOfAnOrganisation	374
Comment received				
We have been using this substance for more than 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any other materials in powder form our workers use appropriate safety equipment to protect themselves from dusty materials. Additionally there is efficient ventilation and extraction installed in the related production areas for reducing the risk of having powder in the air. As soon as Titanium Dioxide has been incorporated in the printing ink, the TiO2 is no more available to be inhaled. But although the classification proposal is for TiO2 as inhalable dust, it would also affect liquid or pasty products and even readymade packaging. This is the consequence of a hazard and not a risk based legislation. ECHA note – A non confidential attachment was submitted with the comment above. doc20160712121001.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	I&P Europe - Imaging and Printing Association e.V.	BehalfOfAnOrganisation	375
Comment received				
Carcinogenicity: Mixtures of toner, printing ink and other imaging related chemical preparations with TiO2 are currently not classified as carcinogens according to the EU regulation 1272/2008/EC due to the presence of TiO2. Despite many years of production and use no cases or (eco)toxicology test results are known which indicate carcinogenicity due to the use of TiO2 in coated films, specialty foils and other imaging and printing related articles. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf				
Dossier Submitter's Response				
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	Weilburger Coatings GmbH	BehalfOfAnOrganisation	376
Comment received				
We have been using this substance for nearly 100 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Japan		BehalfOfAnOrganisation	377
Comment received				
We believe TiO2 does not have carcinogenic potential on humans from following reasons. Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ. The causal relation of the carcinogenicity associated with titanium dioxide has not been reported since titanium dioxide has placed in the market for more than 90 years. In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.				

We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses. We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.
Dossier Submitter's Response
See points 1, 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany		Individual	378
Comment received				
TiO2 could only cause cancer to humans if there was a heavy exposure that would prevent the persons to clear the lungs. This situation is not possible because TiO2 is only processed in working environments where the dust concentration is monitored and controlled according to exposure limits set by law. ECHA note – A non confidential attachment was submitted with the comment above. Comment to RAC of the ECHA Jochen Winkler.docx				
Dossier Submitter's Response				
See points 2, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Australia	Australian Paint Manufacturers' Federation Incorporated	BehalfOfAnOrganisation	379
Comment received				
Refer to the International Paint and Printing Ink Council submission ECHA note – A non confidential attachment was submitted with the comment above. ECHA Proposed Classification of Ti02.pdf				
Dossier Submitter's Response				
See point 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Japan	Japan Cosmetic Industry Association	BehalfOfAnOrganisation	380

Comment received

We believe TiO2 does not have carcinogenic potential on humans from following reasons.
Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ.
The causal relation of the carcinogenicity associated with titanium dioxide has not been reported since titanium dioxide has placed in the market for more than 90 years.
In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.
According to two inhalation studies in rat, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumours, and adenocarcinoma were observed only in female rats, whilst it was not recognized that the increase of carcinogenesis or the increase of mortality in other two studies in rats or a study in mice. In addition, two inhalation studies in rat mentioned above, the study exposed rats to titanium dioxide at concentrations of 0, 10, 50, 250 mg/m3 showed that the maximum dosage caused bronchioalveolar adenoma, and it suggested overloading context (Lee, 1985 R2). It's known that pulmonary responses to inhaled particles of TiO2 differ by species, we consider that it's inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans.

We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses.

We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM. Please note that data were considered sufficient for the classification proposal for carcinogenicity.

RAC's response

Noted. RAC thoroughly discussed the reliability of data for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	BASF	BehalfOfAnOrganisation	381

Comment received

The dossier submitted proposes to classify Titanium dioxide as a carcinogen for the inhalatory route based on experimental findings in rats which occurred under lung

overload conditions and are described to be a generic response of inert particles. The underlying mechanism, specifically in relation to human relevance, has been discussed in depth in the ECETOC Technical Report no. 122 on poorly soluble particles/lung overload published in 2014. The conclusion on the human relevance differs significantly from the assessment by the dossier submitter in that there are strong arguments against the simple transfer of the rat findings to humans. No reference is made to this report in the CLH dossier which is unfortunate since it is the result of intensive discussions among global experts in the field of inhalation toxicology.
The CLH report proposes to classify the substance in category 1B (inhalation) because "…it appears that lung retention and chronic pulmonary inflammation in humans are consistent with the findings in rats". No reference is given for this assumption. Arguments arising from data on Titanium dioxide and poorly soluble substances in general are mixed. In contrast, as described in detail in the ECETOC report no 122, the response by rats to chronic inert particle exposure is considerable different than that of other species. This is reflected in the ECHA guidance on information requirements and chemical safety assessment of 2012 (Appendix R8-15) which states that "The relevance of lung overload in animals to humans is currently not clear and is subject to continuous scientific debate". Most importantly, epidemiology studies did not show a link between Titanium dioxide dust exposure and lung cancer in workers. The epidemiology data were also used for the IARC report (2010) which concluded that there is inadequate evidence for carcinogenicity in humans. Since then, two publications on occupational exposure and mortalities at titanium dioxide production facilities supported the absence of a carcinogenic potential for humans (Ellis ED et al. J Occup Environ Med. 2010 Mar;52(3):303-9; Ellis ED et al. Am J Ind Med. 2013 Mar;56(3):282-91).

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Netherlands	PPG	BehalfOfAnOrganisation	382

Comment received

The Titanium Dioxide Manufacturers Association (TDMA) and the European Chemical Industry Council assessed the TiO2 classification in 2010 under the EU Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation using the same dataset, and on their assessment determined that "TiO2 should not be classified in any of its forms for any endpoints". PPG toxicologists have reviewed the published studies and provide the following comments in opposition to the classification of TiO2 as a carcinogen.

1. Keratinizing cysts, the tumor type observed in rats exposed to high levels of airborne TiO2, do not develop in humans and should not be used to predict human health hazards.

When exposed to high doses of poorly soluble particles, rats develop a range of tumors including adenomas, adenocarcinomas, squamous cell carcinomas and keratinizing cysts (Nikula, 2000). A long term inhalation study in rats exposed to TiO2 (Lee, 1985) reported that 13/74 high dose female rats developed squamous cell carcinomas. A reevaluation of the histopathology by four pathologists using current diagnostic criteria identified 11/13 of the tumors as non-neoplastic pulmonary keratinizing cysts (Warheit, 2006) rather than squamous cell carcinomas. Certain histopathological lesions (i.e., cell types) are observed both in laboratory animals and humans while other lesions may only be observed in one species and not others. Specifically, rats are known to develop keratinizing cysts, while

humans do not (Green 2000). Keratinizing cysts were noted in the rodent inhalation studies cited in the CLH proposal (Lee, 1985; Heinrich, 1995). However, as keratinizing cysts do not occur in humans, these findings should not be used for human hazard assessment.

Table 6. Contrast in cell types between human and rodent lung tumors (from Green [2000])

Tumor type	Human	Rat	Mouse
Keratinizing cysts	No	Yes	Yes
Adenoma	Rare	Yes	Yes
Adenocarcinoma	Yes	Yes	Yes
Squamous carcinoma	Yes	Yes	Yes
Small-cell anaplastic	Yes	No	No
Large-cell anaplastic	Yes	No	No

2. Rats are more sensitive than humans to the development of tumors from exposure to poorly soluble particles and are not an appropriate animal model for extrapolation to human health hazard or risk assessment.

Rats, particularly female rats, are known to develop lung tumors upon chronic exposure to poorly soluble particles, such as TiO2. These tumors occur only at high exposure levels, which result in a phenomena termed "particle overload". Particle overload is defined by impaired alveolar clearance of particles, and in rats, this impaired clearance results in sustained inflammation and oxidative stress. The degree of alveolar inflammation and the resultant epithelial cell proliferation in the rat exceeds that of other rodent species and humans, which may be the cause of the increased susceptibility in rats (Mossman, 2000). Particle overload is believed to be necessary in order for inhalation of poorly soluble particles to result in lung tumors in rats (ILSI, 2000).

Six comparative studies of poorly soluble particles have been conducted in rats and monkeys (Nikula, 2000). These studies have found that both monkeys and rats retain particles in the lungs, but rats retain a greater portion within the intraluminal alveolar macrophages and respond with more epithelial hyperplasia and active inflammation. Conversely, exposure to poorly soluble particles in monkeys results in more interstitialization of deposited particles and less inflammation and epithelial cell proliferation than is observed in the rat (Nikula, 2000). The monkey studies were not life-time studies; however, the studies were 24 months in duration and it is relevant to note that no tumors were reported in the monkeys (ILSI, 2000).

In terms of respiratory tract physiology and particle deposition, humans are more similar to monkeys than to rats (ECETOC, 2013). Epidemiology studies in humans exposed to poorly soluble particles, such as coal workers, have failed to provide definitive evidence of significant increased risk of lung cancer in these workers. An epidemiology study of over 15,000 TiO2 industry workers in Europe did not show an increased incidence of lung cancer in workers exposed to TiO2 (Boffetta et al., 2004). Both the CLH proposal and IARC found inadequate evidence in humans that TiO2 causes lung cancer based on epidemiological studies (IARC, 2010).

3. Exposure levels which resulted in rat lung tumors by inhalation to TiO2 were significantly higher than levels workers are exposed to occupationally.

Lung tumors observed in rats following inhalation of poorly soluble particles occur only at high levels of chronic exposure. For TiO2, significant increases in tumors were observed at a concentration of 250 mg/m3 (Lee, 1985) but not at lower exposure concentrations. The mechanism of action for lung tumor development in the rat requires particle overload, which results in increased oxidative stress (ILSI, 2000). TiO2 is not directly genotoxic; secondary genotoxicity occurs from oxidative stress produced by chronic inflammation and this mechanism has a clear threshold. At exposure concentrations which do not cause chronic inflammation, there is no oxidative DNA damage and therefore no

lung cancer hazard (ECETOC, 2013). Occupational exposure to TiO2 is limited to 10 mg/m3 or less in many countries in the EU (French National Institute of Research and Safety; Ministry of Employment and Social Security of Spain; Ireland National Authority for Occupational Safety and Health). This is well below the level required to cause tumors in rats. Further, since rats are known to be more sensitive than humans to lung cancer from poorly soluble particles, no additional safety factor would be required to extrapolate the no observable effect concentration from rats to humans.

4. The CLP Criteria and the United Nations (UN) Globally Harmonized System for Classification and Labeling (GHS) both state that classification as a carcinogen must be carefully evaluated when the classification is based on animal data from studies employing excessive doses and by modes of action that are not relevant to humans.

As previously stated, female rats develop lung tumors following inhalation exposure to excessive concentrations of TiO2. The mode of action, via particle overload, has not been found to be relevant to humans. The UN GHS states "if a mode of action of tumour development is conclusively determined not to be operative in humans, the carcinogenic evidence for that tumour may be discounted following expert review and weight of evidence analysis" (ECETOC 2013). Both the ECHA guidance on the Application of the CLP Criteria (Version 4.1, June 2015) and the UN GHS also state that "tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard" (UN GHS, 2013). Further, the EU CLP states "…substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification." (ECHA, 2015). Titanium dioxide should not be classified as a 1B carcinogen under the CLP or UN GHS criteria because the lung tumors in female rats occurred only at the site of contact and at extremely high exposure levels and by a mode of action (particle overload) that is not relevant to humans.

References:

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* European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Poorly Soluble Particles/Lung Overload. Technical Report No. 122. December 2013; Brussels.

* European Chemicals Agency. Guidance on the Application of the CLP Criteria. June 2015, Version 4.1. https://echa.europa.eu/documents/10162/13562/clp_en.pdf

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* International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Carbon Black, Titanium Dioxide, and Talc. 2000: Volume 93; World Health Organization. Lyon, France.

* ILSI Risk Science Institute Workshop Participants. The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment: A Workshop Consensus Report. Inhal Toxicol. 2000; 12: 1-17.

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March 11, 2016

* Lee KP, Trochimowicz H.J, Reinhardt C.F. Pulmonary response of rats exposed to titanium dioxide (TiO2) by inhalation for two years. Toxicol Appl Pharmacol. 1985 Jun 30; 79(2): 179-92.

* Ministry of Employment and Social Security of Spain. National Institute for Health and Safety as Work. Occupational exposure limits for chemical agents in Spain. Initially published 1999; Last Edition January 2016

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* Nikula KJ. Rat lung tumors induced by exposure to selected poorly soluble nonfibrous particles. Inhal Toxicol. 2000: 12: 97-119.

* United Nations. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). 2011. Fourth edition.
https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf

* Warheit DB, Frame SR. Characterization and reclassification of titanium dioxide-related pulmonary lesions. J Occup Environ Med. 2006 Dec; 48(12):1308-13.

Dossier Submitter's Response
See points 2 and 4 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Motip Dupli GmbH	BehalfOfAnOrganisation	383
Comment received				
No special case of cancer related to TiO2 has been reported yet.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	WEILBURGER Graphics GmbH	BehalfOfAnOrganisation	384
Comment received				
We have been using this substance for more than 25 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	Aspa-Ingrecos	BehalfOfAnOrganisation	385
Comment received				
Regarding the CLP criteria (regulation 1272/2008), a substance is classified Carcinogenic category 1 (known or presumed human carcinogens) only on the basis of epidemiological and/or animal data ; And the substance may be further distinguished as: Category 1A: known to have carcinogenic potential for humans, classification is largely based on human evidence, or Category 1B: presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. Titanium Dioxide cannot be classified carcinogenic category 1A because human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. Titanium Dioxide would not be classified carcinogenic category 1B because animal data do not constitute an enough strength weight of evidence. Anses's report mentions 4 inhalation route studies on animal : Lee, 1985 ; Heinrich, 1995 ; Muhle, 1989 and Thyssen 1978. Only two out of four show positive results : - In Heinrich's study : impairment of clearance function, bronchioalveolar hyperplasia and interstitial fibrosis observed in female rats ; and not carcinogenic in female mice ; Not guideline, no GLP status study : cannot be scored 1 according to Klimisch - In Lee's study : males and females rats tested : impairment of clearance function, pulmonary inflammation and cell proliferative responses from 50 mg/m3 Similar to guideline, no GLP status : score according to Klimisch ? (probably not 1) Relevance of these higher doses : 50 and 250 mg/m3 compared to doses in the cohort study (Chen et al., 1988) up to 20 mg /m3 level of TiO2 at which workers are exposed. We would like to quote page 51 the following paragraph : ''Based on these studies, IARC (2010) classified TiO2 as possibly carcinogenic to humans (Group 2B) without differentiation between ultrafine and fine TiO2 particles. However, based on the same studies, the NIOSH (2011) concludes that although ultrafine TiO2 should be considered a potential occupational carcinogen, there are insufficient data at this time to classify fine TiO2 as a potential occupational carcinogen since effects were observed at concentration (250 mg/m3) that was significantly higher than currently accepted inhalation toxicology practice. ''				

We are not certain that Lee's study alone can justify the ANSES' proposal to classify TiO2 carcinogenic category 1B. Doses in Lee's study are exceeding the maximum tolerated dose and leads to the overload lung phenomenon which seems normal at these excessive doses (250mg/m3). In consequence, the strength of evidence is too low to consider the ANSES' proposal to classify TiO2 as carcinogenic category 1B by inhalation.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom	Sun Chemical Europe	BehalfOfAnOrganisation	386
Comment received				
The proposal for a carcinogenic classification is based on data obtained during unrealistic testing conditions, whereby the lung clearance mechanism of poorly soluble dust particles is overloaded. This effect is specific to rats, and not relevant for hazard classification for human health or the environment. This is even acknowledged in the ECHA Guidance. In addition, titanium dioxide is a very widely used industrial chemical. There are very large numbers of potentially exposed workers. There is no evidence of carcinogenicity from numerous epidemiological studies. This supports the assertion that the testing under lung clearance overload conditions is not relevant for human health. Inhalation of titanium dioxide particles at doses up to the maximum tolerated dose below the level at which the lung clearance mechanism becomes overwhelmed does not result in the formation of tumours - good evidence for the absence of carcinogenicity. More specific comments can be found in the submission of the Titanium Dioxide Manufacturers Association (TDMA), which we support.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany		BehalfOfAnOrganisation	387
Comment received				
We have been using this substance for 60 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Austria	MUREXIN GMBH	BehalfOfAnOrganisation	388
Comment received				
TiO2 has been used by our company since many years without any indication according to health problems. It is has been also used over decades, in high volumes worldwide and over a broad range of different products, from wall paints to pharmaceuticals, UV blocker(cosmetics) and food packaging. As far as reported and in our own experience, there are no real life incidents that TiO2 has caused cancer in workers. So human data do not suggest an association between occupational exposure to TiO2 and risk for cancer [see also CLH-Report p8]. Based on all facts available now, we are confident that there is no justification for classifying TiO2 as a potential carcinogen.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2016	Austria		BehalfOfAnOrganisation	389
Comment received				
Some institutes evaluated TiO2 as "possibly carcinogenic to humans" on studies in rats. However, it is generally recognized that the rat is uniquely sensitive to the effects of "lung overload" which is not observed in other species including humans.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom		BehalfOfAnOrganisation	390
Comment received				
Based on the information in the dossier it seems that the occasional occurrence of tumors is the secondary consequence of exposure to dust (in some cases lung overload) as a result of inflammation, lesion and other symptoms. This does not suggest intrinsic carcinogenicity. Besides, the primary symptoms are caused by the physical properties ("dustiness") of the substance rather than its chemical nature. There is a concern that if we start classifying carcinogens on this basis then other commonly used, dusty substances will be classed as carcinogenic too and users are going to be "blindened" by it which may result in ignorance. It would defeat the purpose of hazard communication and users may ignore warnings on substances which may be genuinely and intrinsically carcinogenic.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	hubergroup Deutschland	BehalfOfAnOrganisation	391

Comment received
We have been using this substance for more than 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any other materials in powder form our workers use appropriate safety equipment to protect themselves from dusty materials. Additionally there is efficient ventilation and extraction installed in the related production areas for reducing the risk of having powder in the air. As soon as Titanium Dioxide has been incorporated in the printing ink, and even more when e.g. a printed packaging is made from this ink, the TiO2 is no more available to be inhaled. But although the classification proposal is for TiO2 as inhalable dust, it would also affect liquid or pasty products and even readymade packaging. This is the consequence of a hazard and not a risk based legislation. ECHA note – A non confidential attachment was submitted with the comment above. hgD Statement_ECHA_Consultation_TiO2.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Sweden		MemberState	392

Comment received
The Swedish CA supports classification of titanium dioxide (CAS No. 13463-67-7) as specified in the proposal, but feels that it would be desirable to sound out views regarding the possible role of certain physicochemical properties on carcinogenicity as indicated below. Nevertheless, SE agrees with the rationale for classification into the proposed hazard class and differentiations. We agree that the available data show that titanium dioxide is carcinogenic via the inhalation route of exposure and should be classified accordingly. Regarding the issue whether this effect of titanium dioxide occurs whatever its physicochemical properties may be, we think there is evidence that both nanoparticles and microparticles as well different crystal phases induce tumours, supporting that titanium dioxide is carcinogenic irrespective of particle size and crystal phase. However, there are no tumour data available to enable an evaluation of the impact of particle coating and the impact of particle shape on carcinogenicity. In the CLH report, the arguments for concluding that titanium dioxide is carcinogenic irrespective of coating and particle shape are based on data showing that various coatings and shapes of particles of titanium dioxide induces chronic inflammation and oxidative stress, and that tumours could be induced secondary to these effects. We think that the strength of the evidence for this view should be further clarified and discussed.

Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany	Ostchem Germany GmbH as OR	BehalfOfAnOrganisation	393
Comment received				
Therefore, we do not see any necessity to re-evaluate titanium dioxide from category 2B to «inhalation Cat 1b carcinogen».				
Dossier Submitter's Response				
Please note that although there is a strong link between CLP and IARC classification criteria regarding the definition of "evidence", interpretation of "sufficient" and "limited" can differ. Furthermore, additional criteria are taken into account in CLP decision. Finally, IARC classification has no regulatory impact.				
RAC's response				
Noted. The RAC opinion compares the conclusions of the IARC assessment with the RAC proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France		BehalfOfAnOrganisation	394
Comment received				
The problem is that there is no epidemiological data in ANSES report. How can we determine the carcinogenicity 1B by inhalation? What is the link between epidemiological results and animal data because it seems to be not to have a link between both in the report. We do not use Titanium dioxide as UV filter in spray today. Titanium dioxide we use in spray is the pigmentary form only for fluid foundation.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM. Please note that epidemiological data is reported in CLH report from page 38.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Japan		BehalfOfAnOrganisation	395
Comment received				
We believe TiO2 does not have carcinogenic potential on humans from following reasons. Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ. The causal relation of the carcinogenicity associated with titanium dioxide has not been				

reported since titanium dioxide has placed in the market for more than 90 years.
In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.
According to two inhalation studies in rat, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumours, and adenocarcinoma were observed only in female rats, whilst it was not recognized that the increase of carcinogenesis or the increase of mortality in other two studies in rats or a study in mice. In addition, two inhalation studies in rat mentioned above, the study exposed rats to titanium dioxide at concentrations of 0, 10, 50, 250 mg/m3 showed that the maximum dosage caused bronchioalveolar adenoma, and it suggested overloading context (Lee, 1985 R2). It's known that pulmonary responses to inhaled particles of TiO2 differ by species, we consider that it's inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans.
We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses.
We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM. Please note that data were considered sufficient for the classification proposal for carcinogenicity.

RAC's response

Noted. RAC thoroughly discussed the reliability of data for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Italy	Laterlite S.p.A.	BehalfOfAnOrganisation	396

Comment received

no, see attachment for details

ECHA note – A non confidential attachment was submitted with the comment above.
2016-07-15 laterlite reply to public consultation on TiO2.pdf

Dossier Submitter's Response

See point 1 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	EuPC (European Plastics Converters	BehalfOfAnOrganisation	397

Comment received

The French agency ANSES is proposing a new harmonised classification for Titanium dioxide as a "potentially carcinogenic to humans" (Category 1B) / "may cause cancer by

inhalation"(H350i).
The basis of this proposal for classification as carcinogen by inhalation comes from a limited number of animal studies. ANSES continues explaining that" (as other non soluble dusty material), TiO2 is considered poorly soluble particles and the main proposed mechanism of carcinogenicity by inhalation is thus based on the low solubility and biopersistency of the particles leading to pulmonary inflammation then oxidative stress."

TIO2 has been used safely for decades. This is supported by the findings of epidemiology studies of 20,000 workers in 15 Titanium Dioxide manufacturing plants over several decades which showed no adverse health effects from occupational exposure. In a recent survey across the plastics converting and masterbatching industry, we did not gather evidence of workers health issues related to the use of TIO2.

The ANSES conclusions cannot be corroborated by epidemiological studies and relies only on few animal studies.
All relevant guidance documents by ECHA, OECD and ECETOC-Report unanimously observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons. Therefore, a classification is neither justified nor appropriate from the toxicological perspective. For justification purposes, we refer to CLP regulation Annex I, 3.9.2.8.1.(e).
"substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification."
The carcinogenic effect found exclusively in animal testing is based on particle-caused inflammatory processes in the lungs due to dust exposure by inhalation. However, this is not substance-specific for titanium dioxide but characteristic of a large amount of dust, irrespective of the underlying substance.
Finally, the studies used for supporting classification were either of inferior quality or using extreme doses, which have no relation to real or even extreme conditions of exposure (exposures went as high as 120 or even 250 mg/m³, whilst general regulation limiting dust in plan range from 4 to 10 mg/m³. As will be seen below we expect even lower exposures in practice*). For further discussion of the effects refer to the detailed comments submitted by TDMA and TDIC.
*The recent information collected on general workplace air concentration exposure in the plastics masterbatching and converting industry showed that companies are monitoring the dust concentration and the measured level are usually below the DNEL 10 mg/m³ and generally much lower. Moreover, in critical steps such as debagging, workers are equipped with body protection and with respiratory masks, in most cases of FFP2 or FFP3 type, which give a protection factor 10 or 20.

ECHA note – A confidential and a non confidential attachment were submitted with the comment above.
2013-07-15_TiO2 CLH comment EuPC_confidential.pdf
2013-07-15_TiO2 CLH comment EuPC_public.pdf

Dossier Submitter's Response
See points 1, 2, 4 and 5 of attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	European Expanded Clay Association	BehalfOfAnOrganisation	398

Comment received
A classification as cat. 1 carcinogenic can only be justified on the basis of sound scientific evidence, which is not the case in the CLH report ECHA note – A non confidential attachment was submitted with the comment above. 16 07 15 Cerame-Unie comments to the proposed classification of TiO2.docx
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Cerame-Unie - The European Ceramic Industry Association	BehalfOfAnOrganisation	399
Comment received				
Cerame-Unie, the European Ceramic Industry Association, fully supports the general and specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA), the Titanium Dioxide Industry Consortium (TDIC) and the Industrial Minerals Association (IMA-Europe).				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Belgium		BehalfOfAnOrganisation	400
Comment received				
We fully support the scientific position provided by TDMA/TDIC.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	GSB International	BehalfOfAnOrganisation	401
Comment received				
GSB has 47 members (powder and liquid coating manufactures) and 98 members (coaters) in more than 20 EU member states. Since GSB was founded in 1977 we are not aware of any relation between the use of TiO2 and the development of cancer by workers employed by our member companies. When handling TiO2 in powder form or when handling any powder the member companies´ workers use suitable safety equipment to protect them from dusty materials.				

In the coating TiO2 is no more available to be to be inhaled.
Dossier Submitter's Response
See points 2 and 4 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	IBIDEN Porzellanfabrik Frauenthal	BehalfOfAnOrganisation	402
Comment received				
We aim to keep dust emission at workplaces below 5mg/m3. Workers exposed to dust were under medical control by internal and external medical experts using X-ray investigation of lung and lung function test. So far, there was no indication on lung disease related with exposure to dust from our production processes.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	Wirtschaftskammer Österreich (WKÖ)	BehalfOfAnOrganisation	403
Comment received				
Please, see document attached. ECHA note – A non confidential attachment was submitted with the comment above. su_133_StN_WKÖ Titanoxid.pdf				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States		Individual	404
Comment received				
Some specific comments: Page 8, first full para. dealing with carcinogenicity of TiO2: The report states that TiO2 "behaves as other poorly soluble low-toxicity particles (e.g., coal dust, diesel exhaust particulates, toner ….)". An interesting statement to confirm what is generally accepted by the scientific community, with the exception of diesel exhaust, which is no longer considered as a PSP by MAK or in the US. The next paragraph on same page likewise points out that human data do not show an association between occupational exposure to TiO2 and cancer; then the limitations of epi studies in terms of misclassification are mentioned which, however, later in the document				

is not well-substantiated.
Last para., same page: Here as in several other places in this document it is stated that "An inflammatory process and indirect genotoxic effect by ROS production seems to be the major mechanism to explain the effects induced by TiO2". This is followed by the statement that a direct interaction with DNA cannot be excluded because TiO2 was found in the cell nucleus in various in vitro and in vivo studies. Regarding these in vitro studies, these are short-term studies at doses of very questionable relevance to in vivo situations, with no confirmation of the identity of intranuclear inclusions via EDX analysis. Neither the Jugan et al. nor Shukla et al., publications of in vitro studies provide high enough magnification to confirm TiO2 in the nucleus. The investigators failed to use an insert image at 150 000 magnification to show the details of the particles for comparison to the original particles alone. The Tavares et al. study did not really show TiO2 in lymphocytes exposed in vitro. The only in vivo study by Louro et al., showed TiO2 (?) in mitochondria, again no EDX analysis was performed or higher magnification provided to confirm that it is really TiO2.

Page 27, last para., Intratracheal route: It would be important in the context of summarizing intratracheal bolus-type administration studies to critically discuss the limitations of such bolus-type dosing in rodents: A huge dose is administered within a fraction of a second which normally (by inhalation) takes days or weeks or even longer to accumulate slowly in the lung. This means, the dose as well as the dose-rate becomes a very important factor due to overwhelming normal defenses and activating mechanisms which are not operating at realistic doses. Paracelsus' famous phrase: "the dose makes the poison" needs now to be extended to: " the dose also makes the mechanism" (Slikker et al., 2004). Any intratracheal instillation delivery clearly exceeds by far any realistic inhalation exposure under real-world conditions. As discussed by an expert working group (ILSI, 2000), bolus-type (intratracheal instillation, oro-pharyngeal aspiration) administration, is limited to hazard identification, but cannot be used for risk characterization. These important severe limitations associated with bolus-type studies and the interpretation of such results should be critically discussed as part of the background information for the CLH document.

In general, a critical analysis of conclusions drawn by the authors of the CLH proposal is missing which would be helpful to inform the reader, for example, in the next to last paragraph on page 29 which summarizes Xu et al. Similarly, the section on page 32, which contrasts tumor induction of fine vs. ultrafine TiO2 by suggesting a higher translocation of the nano-sized TiO2 into interstitium, neglects to compare the dosemetric "surface area" between the two types of TiO2 which would fully explain the different tumor incidences.

On the same page 32, the last paragraph suggests that the particle-volume metric is the most adequate one for the carcinogenicity of PSP, which disregards newer findings with regard to the importance of the surface area metric for correlating effects induced by particles of poor solubility and low cytotoxicity (PSP). In the 19-dust study discussed on this page (32), the amount of retained TiO2 in the lung was not measured and confirmed. The limitations of this particular intratracheal study need to be clearly pointed out with respect to the unrealistic excessive doses administered as a bolus.

Page 45, last para., Baggs study: Here again, a statement is made that nano- TiO2 has greater biological activity than fine TiO2, which of course is based on the metric "mass" which is not appropriate for comparing effects of different PSPs. As has been shown in several studies, normalizing and expressing the dose as particle surface area shows that different sizes of TiO2 fall on the same dose- response curves.

Page 49, top two lines: I don't think that the statement "epidemiological data are considered inadequate" is part of a conclusion by IARC; rather, the conclusion is that the evidence based on epidemiological data is inadequate.
Next to last para.: The reason that no lung tumors were reported in the Muhle studies is that concentrations/doses used - although still rather high -, are lower and more realistic and, therefore, no carcinogenic effects in rats were observed despite potential impaired particle clearance due to overload. As mentioned before, this is in stark contrast to the excessively high doses administered in "positive" inhalation/instillation studies. Any PSP at such excessive doses will induce lung tumors in rats when chronically exposed, but not in other rodents.

Page 50, bold-faced para.: An "acceptable quality" of the one inhalation and one intratracheal study is mentioned here, and it needs to be made clear that this "acceptability" only refers to the technical performance of the study but not to the "scientific appropriateness" in terms of realistic/relevant doses. It would be fitting to address the general drawback in the proposal of not discussing the relevance, or better irrelevance, of many studies. A well-designed toxicological study would employ at a minimum three concentrations from which the slope of a dose-response relationship can be derived and where the maximum concentration should not exceed an MTD or MFTD (Oberdörster, 1995).

Page 50, last full para.: Statements about more likely achieving volumetric overload with nanoparticles compared to fine particles does not make sense. It is encouraging, though, that the subsequent sentences in this paragraph referring to Borm et al. (2004) address the issue of greater specific surface area and associated reactivity and that the higher effect of nanoparticles relative to fine particles is just based on the metric "mass", yet when expressed as surface area there is no difference. This addition in this paragraph is encouraged. See also discussion of the mass vs. surface area overload concept in Borm et al. (2015).

Page 51, upper para.: The concept of the importance of dosemetrics is well addressed in this paragraph by the statement that the mass-metric is not the best metric for nanoparticles. Therefore, a comparison based on mass will not be appropriate to conclude a higher toxicity of one form over the other. For clarification, including the metric "surface area" would be helpful. (See comment above).

In contrast, though, two paragraphs below on the same page, the conclusion is that a higher carcinogenic potential of ultrafine TiO2 can be suggested from these studies. Although this cannot be confirmed, the authors cite as reasons differences in route-of-exposure, concentrations, duration, etc. This is hard to understand, and requires clarification.

In contrast, the next paragraph on page 51 is more meaningful, explaining the IARC (2010) classification for TiO2 and the NIOSH conclusions.

The following pages 52-56 discuss the impact of different characteristics on carcinogenic potential, again without emphasizing the critical importance of excessive vs. realistic dosing concepts. For example, a study by Pott and Roller with coated nano-TiO2 vs. uncoated TiO2 with a huge total dose of 15 mg instilled in rats showed a high acute toxicity with the coated TiO2 resulting in high mortality. In contrast, when Oberdörster (2001) used the same material at a much lower dose (0.5 mg, instilled), the coated TiO2 induced a much lower pulmonary inflammation compared to the uncoated TiO2 .

Page 57, last para.: The translocation pathway from the lung to the pleura is not only

operating for fibers but is a general clearance pathway for all particles; the difference being that spherical particles will easily be cleared from the pleural cavity via lymphatic stomata, whereas fibrous particles greater than ~10 - 20µm may not be able to enter these lymphatic passages in the parietal pleura.

Page 58, bold-faced para.: Biopersistence and poor solubility is emphasized here as the most important factors in TiO2 induced lung tumorigenicity. However, the over-arching most important parameter is excessive doses of PSP delivered to the lung, doses which have no relevance whatsoever for real-world exposure conditions in humans.

Lower para. on page 58: Again, the excessive dose issue is not part of the description of the mode of action and the statement that biopersistent particles of poor solubility cannot be fully phagocytized by the macrophages applies only when excessive doses are deposited. Without excessive doses, PSP are well-phagocytized, but with excessive doses they can overload the macrophages and induce a pro-oxidant inflammatory condition overwhelming the cells' defenses and thereby impairing macrophage clearance function. This results in significant interstitialization of non-phagocytosed particles with all the subsequent pathogenic mechanisms involving secondary ROS induced genotoxicity leading to epithelial cell proliferation and mutagenesis.

Page 59: Genotoxicity of TiO2 is addressed here, summarizing that only one in six experiments in in vivo studies were positive in the comet assay. As one would expect, in vitro studies showed much greater (~50%) positive results with respect to the micronucleus and other tests. Again, the issue of dose, bolus-type delivery and unrealistic exposure conditions are all important factors to consider here, particularly for the in vitro studies.

Same page, Mechanisms of toxicity: In this context and with regard to secondary genotoxicity, a study by Driscoll et al. (1997), referenced in this document, nicely demonstrated that the inflammatory cells, particularly PMN, induced by high loads of cytotoxic as well as low toxicity particles caused HPRT mutations in alveolar epithelial cells due to oxidative stress; induction of mutations could be inhibited by antioxidants, confirming an underlying ROS mechanism of secondary genotoxicity.

Page 60, several comments: The German MAK value for GBS particles is addressed, it should be pointed out here that the MAK recommended value is very different from the NIOSH REL, namely 0.5 (MAK) vs. 2 (NIOSH) mg/m3. Also, the conclusion from the German MAK document, although generally appropriate, does not mention excessive doses as explanation for the positive rat studies. Particle overload per se does not necessarily result in tumor induction in rats, it is only when the overload doses are highly excessive, as discussed earlier in these comments. Furthermore, the final conclusion that "All GBS are carcinogenic to humans with a threshold effect" should be presented as hypothesis. There is no epidemiological or otherwise evidence confirming this statement.

Page 61, top para.: With respect to extrapolation of overload-induced rat tumors to other species, it should be mentioned that as previously addressed, coal miners despite highly overloaded lungs showing prolonged particle clearance (Freedman and Robinson, 1988; Stöber et al., 1993) have not shown carcinogenicity in epidemiological studies, and that rats exposed to coal dust did induce lung tumors in overload conditions (Martin et al., 1977). Such interspecies differences in terms of inducing overload-based lung tumors need to be emphasized, demonstrating the greater susceptibility of rats to respond with lung tumors in contrast to humans (and mice!) under extreme lung overload conditions with the same type of particles.

B. Dosimetric Analysis of 2-Year Rat Inhalation Study and Human Extrapolation

In order to demonstrate differences between rats and humans with respect to clearance and retention of inhaled PSP, the following analysis of the Lee et al. two-year rat inhalation study with TiO2 (Lee et al., 1985; 1986) for deriving a Human Equivalent Concentration (HEC) was performed.

For the dosimetric analysis of the Lee et al. 2-year inhalation study the widely accepted Multiple Path Particle Dosimetry (MPPD) model was used which predicts the deposition and clearance of inhaled particles in the rat and human respiratory tract (https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304) and which is based on many published peer-reviewed data of respiratory tract structures and of results of inhaled particle deposition and retention kinetics in different mammalian species. This model is very versatile in terms of simulating different breathing scenarios and particle size distributions. The present analysis – using the most recent MPPD Version 3.04 – focuses mainly on the 50 mg/m3 (mid-concentration) and only on male rats of the 3 exposure groups of the 2-year rat study. Only a succinct summary of the dosimetric concepts and calculations will be presented here, however, I would be happy to discuss details if needed.

Summary data of 2-year study of inhaled TiO2 and of some results relevant for this analysis:

Aerosol: MMAD: 1.7 µm; GSD: 2.52; Conc: 50 mg/m3; effective density, d(eff): 0.7 g/cm3 (TiO2 material density of 4.2 g/cm3 was also compared d(eff) has to be used because the aerosol consisted of agglomerated primary particles with void spaces between them)

Exposure: Whole-body; 6 hrs/day; 5 days/week; for 2 years

Rats: Crl: CD rats; bodyweight of male rats: 460 g (start) - 782 g (end); average BW: 700 g

Allometrically adjusted respiratory parameters for MPPD input:
Tidal volume: 5.2 ml
Breathing frequency: 91/min
FRC (functional residual capacity): 5.56 ml
URT (upper respiratory tract): 0.72 ml

Retained lung burden by ICPMS at end of 2-year exposure to 50 mg/m3: 124 mg

Lung weight at end of exposure: exposed rats: 4.38 g
control rats: 3.2 g

Normalized retained lung burden: per g lung of exposed rats: 28.3 mg/g
per g lung of control rats: 38.7 mg/g
(expressing retained dose per g control lung is needed for extrapolation modeling to humans to avoid inaccurate comparison with inflammation-induced increased lung weight)

MPPD modeling results for the rats:

Deposition fractions (DF) of inhaled TiO2:
alveolar region: 3.12%
tracheobronchial: 0.99%
head region: 69%

Daily deposited dose, a:
(a = minute ventilation x exposure conc x dep fraction x exposure mins)
a = 2.66 µg

Retained lung burden (At) after 2 years of exposure, 6 hrs/d, 5 d/wk, assuming normal physiological (unimpaired) lung clearance for rats at a clearance rate of 0.01/day (equivalent to T½ [retention halftime] of 70 days)
At50 = 19 mg (for 50 mg/m3 exposure group)

This calculation was also done for the other exposure groups and results expressed in the following table:

Retained Lung Burden After 2-Yr Exposure		
Exposure Conc	Measured in study	Predicted by model
mg/m3	mg/lung	mg/lung
10	26.5	3.8
50	124	19
250	665	95

This result clearly shows that all three TiO2 exposure concentrations resulted in significant lung particle overload, i.e., an impaired alveolar macrophage-mediated particle clearance function. Per g lung weight, the retained normalized lung burden observed in the study of 28 mg/g exposed lung and 39 mg/g control lung for the 50 mg/m3-exposed rats (shown at the beginning of this analysis, p.7) is obviously greatly exceeding a retained lung burden of 1 mg/g lung which - according to Morrow (1988) - signals the beginning of lung overload in rats. This result also shows that despite a significantly PSP overloaded lung in this 2-year inhalation study lung tumors were only induced at the most excessive lung overload resulting from 250 mg/m3 exposure which is beyond any relevant realistic exposure scenario. While such excessively overloaded lung – as expected – resulted in the induction of lung tumors in the rat, the result also demonstrates that overload conditions below that highly unrealistic excessive level did not induce lung tumors in rats after chronic 2-year inhalation exposure.

Human extrapolation modeling:

Figure 1 (see attached document) shows the concept of interspecies (rat to human) dosimetric extrapolation modeling. The HEC is equivalent to the rat inhaled concentration in terms of resulting in the same retained dose (normalized by lung weight or by lung epithelial surface area) in both species after an acute, subchronic or chronic exposure. This does not necessarily mean that effects will be the same, because it depends on species-specific mechanistic differences how rats or humans are responding to the same insults. Thus, if the goal is to derive a "safe" occupational exposure limit value (OEL) certain safety or assessment factors need to be included. The goal of this analysis, though, is to determine an HEC for exposure of workers that would, during a 40-year occupational exposure, reach the same normalized lung burden as was found in rats after two years of exposure to 50 mg/m3.

The following steps were performed, using the MPPD Version 3.04:

1. Determine lung deposition fractions in humans for same particle size distribution (MMAD; GSD) used in the rat study. (If MMAD and GSD for actual human occupational settings would be known, this would be an even better and ideal extension of this analysis [Oller and Oberdörster, 2016]).

2. Breathing parameters were selected for light exercising conditions of the workers with TV = 1025 ml and breathing frequency of 20/min.

3. The exposure is for 8 hrs/day, 240 days per year (after subtracting weekends, holidays, vacation), for 40 years.
4. The clearance rate in the lung is based on Gregoratto et al. (2010) considering total lung retention (interstitial plus alveolar compartment), with a clearance rate of 0.0017/day (equivalent to a T½ of 400 days).

Results of human extrapolation:

Deposition fractions of inhaled TiO2 particles:
Alveolar = 7.9%; tracheobronchial = 3.01%; head = 53%
Daily deposited dose: 39 mg
Accumulation over 40-year worklife exposure: 15,034 mg
For 1 kg human lung: 15 mg/g lung

Comparing results of the experimental rat (2 years, 50 mg/m3) study and the worker (40 years, 50 mg/m3) model results:

Workers are predicted to accumulate 15 mg/g lung
Rats retained in the 2-year study 39 mg/g control lung (with impaired clearance) or, predicted if no impaired clearance had occurred: 5.9 mg/g control lung

In order for workers to accumulate the same normalized lung burden of 39 mg/g, the HEC has to be: 130 mg/m3 (obviously, that would result in severe pathology and disease)

An HEC to achieve a lung burden which induces no lung pathology would be below the rat's 10 mg/m3 level; however, this needs to be derived using BMD (Benchmark Dose) modeling of the rat study results.

Conclusions

These dosimetric analyses show:

— overload PSP-induced lung tumors in rats are induced only at unrealistic, highly excessive lung burdens

— lower retained PSP lung burdens, still at particle overload conditions with impaired clearance, do not induce lung tumors in rats

— lowering inhaled PSP concentrations to levels not causing inflammation will definitely prevent lung tumors and non-neoplastic lung pathology in rats

— an HEC of more than 100 mg TiO2/m3 of occupational exposure would have to be present long-term to reach lung burdens equivalent to a highly TiO2 overloaded rat lung (2-year rat exposure to 50 mg/m3) without inducing lung tumors. This would clearly

result in severe non-neoplastic effects in workers.

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Additional Remarks:

If instead of the average rat BW (700 g) the maximum final BW (782 g) at the end of the 2-year rat exposure is used to determine allometrically the respiratory rat parameters, the modeled lung burden of
19 mg would increase by 6%.

If instead of the effective TiO2 aerosol density of 0.7 g/cm3 the TiO2 material density of 4.2 g/cm3 is used in the model, the alveolar deposition fraction in rats would increase form 3.12% to 4.83%; the modeled 2-year accumulated lung dose for the 50 mg/m3 exposure group of rats would increase from 19 mg to 29.4 mg, and the normalized lung burden from 5.9 mg/g control lung to 9.2 mg/g control lung. The HEC for workers – using TiO2 material density in the model for both rats and humans – to reach the same normalized lung burden (equivalent to 50 mg/m3 exposed rats) would not change much (from 130 mg/m3 to 128 mg/m3). The overall conclusions summarized above would not change.

References:

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ECHA note – A non confidential attachment was submitted with the comment above.
CLH Report Comments_Oberdörster 7 15 16.pdf

Dossier Submitter's Response

See points 1, 3, 2 and 4 of the attachment to the RCOM.

Regarding proposed classification based on non-neoplastic effects:
Due to ongoing discussions on adequate metrics for nanomaterials, it is not clear if comparison to cut-off values for STOT RE classification is relevant to TiO_2 as nanoparticles. Since the proposed classification as carcinogen is judged appropriate for TiO_2, the resulting risk mitigation measures would cover those induced by a STOT RE classification. Thus, it was not deemed necessary to assess if criteria for STOT RE are fulfilled.

RAC's response

RAC was mandated to give an opinion on carcinogenicity. RAC did not discuss a STOT RE classification.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom	British Coatings Federation	BehalfOfAnOrganisation	405

Comment received

Our members report that over the last 40 years that they have used paints and inks containing titanium dioxide and also titanium dioxide pigment in powder form without any reported cases of cancer. Companies have used these products with appropriate precautions, including local exhaust ventilation and personal protective equipment. The majority of use has involved the use of titanium dioxide bound in either an ink or paint and no risk from titanium dust is perceived. Similarly the finished wallcovering contains bound titanium dioxide and exposure to the finished product does not pose a carcinogenic risk.

ECHA note – A non confidential attachment was submitted with the comment above.
Titanium dioxide comments July 16.docx

Dossier Submitter's Response

See points 1, 2, 4 and 5 of the attachment to the RCOM.

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United Kingdom		Individual	406

Comment received

Experimental studies in rats show that TiO2 is a "nuisance dust" when inhaled at low concentrations. It is inevitable that by inhaling insoluble material from an environment containing 250mg.m3 insoluble material, non-specific pulmonary obstruction, inflammation and stress will occur. Previous studies have adequately demonstrated that persistent inflammatory changes promote release of cytokines and chemical mediators, free radicals and changes conducive to genotoxicity, progressing to frank carcinogenicity (Ferin et al, 1992, Yoshiura et al, 2015; Roberts et al 2011). This seems to be specific to the rat, some strains of which are prone to idiopathic tumours in the lung and other tissues (IARC Publication, Lyon, 1990). These are promoted by long-term stress related hormones. It should be concluded that carcinogenic changes in rats exposed to high levels of TiO2 are not specific and are commonly reported with other insoluble nuisance particulates. The effects are a function of particle size and surface area and are mediated by a "secondary genotoxic mechanism" (Mohr et al, 2006; Warheit et al, 2005, 2007). Histological evidence of lung overload must be a feature of profound respiratory insufficiency and stress.

The rat differs markedly from humans in its shallow breathing patterns and airway physiology and is thus an imperfect model in which to assess pulmonary carcinogenicity from excessive TiO2 inhalation (Corley et al, 2012). The pulmonary pathology presented in the six principal experimental studies in rats in the CLH Proposal is not characteristic of that reported in epidemiological or human case reports.

In 1988 NIOSH recommended that TiO2 exposure be classified as a potential carcinogen on the basis of experimental studies in rats. Lung tumours were observed in animals inhaling TiO2 chronically from closed environments containing 250mg.m3, or following repeated intratracheal instillations (Heinrich et al, 1995; Lee et al, 1985, 1986; Pott & Roller, 1995; Thyssen et al 1978; Trochimowicz et al, 1988; Warheit et al, 2006, 2007). Carcinogenicity was influenced by particle size and surface area as seen with anatase and rutile isoforms. Histological illustrations revealed a massive accumulation of TiO2-containing alveolar macrophages and alveolar cells, persistent pulmonary inflammation and tracheitis. This overload pathology associated with increased benign and malignant tumours, is characteristic of inhalation of vast quantities of insoluble material where natural clearance mechanisms are overwhelmed. It is not specific to TiO2.

ECHA note – A non confidential attachment was submitted with the comment above. Comments on CLH proposal from A Lansdown.pdf

Dossier Submitter's Response

See point 2 of the attachment to the RCOM.

Specific response on references linked to human data:

Garabrant *et al*., 1987, Moran *et al*., 1991 and Keller *et al*., 1995 are not clearly described in the CLH report but are included in the statement page 38 of the CLH report since these human cases are already summarized in the IARC monograph: "Other case reports were summarized in IARC monograph vol. 93 and NIOSH Current Intelligence Bulletin (CIB) 63.

None of these case reports provided quantitative industrial hygiene information about workers' TiO2 dust exposure. Deposits of titanium dioxide in lung tissue as well as in lymph nodes were found. Non-neoplastic respiratory effects were observed in workers, including decline in lung function, pleural disease with plaques and pleural thickening and mild fibrosis changes. More severe reactions were observed in a few cases. However, the workers in these studies were also exposed to asbestos and/or silica." Parkes *et al.* (1977) and Liao *et al.* (2008) do not assess the potential link between TiO_2 and carcinogenicity. Although they might inform on the plausibility of human exposure, they have many limitations and would not change the proposal. Thus, it was not deemed necessary to include them in the CLH report. Ellis publications are taken into account in the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Germany	Stockmeier Urethanes GmbH & Co. KG	BehalfOfAnOrganisation	407
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See reponse to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Eurocolor	BehalfOfAnOrganisation	408
Comment received				
We support the detailed toxicological assessment of the TDMA (Titanium Dioxide Manufacturer Association) and the TDIC (Titanium Dioxide Industry Consortium) ECHA note – A non confidential attachment was submitted with the comment above. Eurocolour input CLH Titanium dioxide_20160712.pdf				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM and reponse to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	DAW SE	BehalfOfAnOrganisation	409
Comment received				
DAW SE has been using TiO2 for more than 55 years in growing amounts, and there is no incidence of any relation between the use of TiO2 and the development of cancer among				

our employees, particularly among our workers dealing with TiO2 in storage, transport or mixing processes. When manually handling TiO2 in powder (from bags/bigbags) form or when handling any powdery material – regardless if it contains TiO2 or not – our workers are equipped with it and use appropriate safety equipment to protect them from dust. After TiO2 has been filled into mixing vessel or into tanks and also in the final liquid or pasty product it is no more available to be inhaled.
Dossier Submitter's Response
See points 1, 2 and 4 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Verband der Mineralfarbenindustrie e.V.	BehalfOfAnOrganisation	410
Comment received				
We support the detailed toxicological assessment of the TDMA (Titanium Dioxide Manufacturer Association) and the TDIC (Titanium Dioxide Industry Consortium) ECHA note – A non confidential attachment was submitted with the comment above. VdMi input CLH Titanium dioxide_20160712.pdf				
Dossier Submitter's Response				
See points 1, 2, 4 and 5 of attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom	Cristal Pigment UK Limited	BehalfOfAnOrganisation	411
Comment received				
Cristal is in complete agreement with the Specific Comments made in the TDMA/TDIC response to this consultation submitted on 14th July 2016.				
Dossier Submitter's Response				
See reponse to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Denmark	Beck & Jørgensen A/S	BehalfOfAnOrganisation	412
Comment received				
Please see attachment ECHA note – A non confidential attachment was submitted with the comment above. Indsigelse mod klassificering af Titandioxid som kræftfremkaldende.pdf				

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	Kuhmichel Abrasiv GmbH	BehalfOfAnOrganisation	413

Comment received

Dear Sir or Madam

Since nearly 40 years Kuhmichel is selling worldwide high-quality reusable blasting, grinding and cutting abrasives to the automotive industry, medical and aerospace engineering and to manufactures, for example of grinding wheels.

TiO2 is part of an artificially material, the corundum. In context with our quality management this product is analysed regarding toxic and crystalline compounds as well as carcinogenicity. These investigations show that no health effects occurs from TiO2 as it is integrated into the crystalline lattice of the corundum.

Kuhmichel is regularly analysing the properties of corundum since many years. Please find attached different expertise over a period from 2004 of the Institute for Occupational Safety and Health of the German Social Accident Insurance (DGUV) for your information.

Due to its properties TiO2 cannot be substituted by another substance with corundum. Corundum is manufactured from bauxite which contains TiO2 geogenically therein; it is not artificially or separately added.

A classification of TiO2 as carcinogenic would significantly increase handling and administrative efforts for all parties concerned, although TiO2 in corundum causes demonstrably no health disadvantages.

Kuhmichel is committed to health and environmental protection. This is also evident from our voluntary product information (for example see Appendix)worked out for each product from our portfolio.

Kuhmichel is represented with legal entities and storage facilities in Germany, Netherlands, Great Britain, Austria, Hungary, Turkey and South Africa. If necessary, each company is able to give this statement individually.

ECHA note – A non confidential attachment was submitted with the comment above.
Gutachten.zip

Dossier Submitter's Response
See point 5 of attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	414
Comment received				
Keine Erkrankung bekannt				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	REHAU AG + Co.	BehalfOfAnOrganisation	415
Comment received				
The anatase form and the rutile form of titanium dioxide should not be mixed up considering supposed carcinogenic properties. The study mentioned on page 24 of the CLH report refers to 80% anatase in form of nanoparticles. This study cannot be used to assess the properties af a standard grade containing 99% rutile.				
Dossier Submitter's Response				
See point 1 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany	Verband der Chemischen Industrie e.V. (VCI)	BehalfOfAnOrganisation	416
Comment received				
VCI Statement on the Proposal for a Harmonised Classification of Titanium dioxide The proposed classification and labelling is inappropriate for the following reasons and would have serious and disproportionately negative impacts: 1. No indications of problems from epidemiological studies and application practice Titanium dioxide has been used safely for many decades. No increased incidence of lung cancer has been observed. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report: "Human data do not suggest an association between occupational exposure to TiO2 and risk of cancer […]" [CLH Report, page 8]. 2. Animal studies cannot be transferred to humans The classification proposal in the CLH report is based essentially on studies in rats exposed to extremely high concentrations of titanium dioxide dusts, which led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and the ECETOC Report unanimously observe that the results from "lung overload" studies in rats should not be transferred to humans for several reasons. Therefore, a classification is neither justified nor appropriate from the toxicological perspective. 3. Existing legislation provides sufficient safety The carcinogenic effect found exclusively in animal testing is based on particle-caused				

inflammatory processes in the lungs due to dust exposure by inhalation. However, this is not substance-specific for titanium dioxide but characteristic of a large number of dusts, irrespective of the underlying substance.
Exposure by inhalation to titanium dioxide can be expected primarily at the workplace. Consequently, relevant dust limit values are in place in several EU Member States. In Germany, there are additionally a number of provisions for further-going protection measures to minimise dust exposure. At the European level, dust exposure could be regulated in a binding and uniform manner in the directives on occupational health and safety. A classification of titanium dioxide is not necessary for this purpose.
4. Major and disproportionately negative impacts due to automatic reference to classification and labelling in existing legislation
In many sets of legislation – e.g. on industrial plant safety and environmental or consumer protection or special legislations on biocidal products or cosmetics – classification and labelling give rise to comprehensive obligations and bans or restrictions, automatically and without any further examination of whether the use of the substance really poses risks. For example, mixtures (like titanium-dioxide containing white wall paint) could be no longer placed on the market for private end consumers.
5. No suitable alternatives are available
Because of the outstanding properties of titanium dioxide regarding health, safety, environment and performance, no suitable alternatives are available. As the carcinogenic effect in animal testing is not substance-specific but characteristic of dusts, this can be expected to occur with all potential alternative substances too.
6. Considerable negative impacts in all industrial sectors
Because of its outstanding properties, titanium dioxide is an all-rounder raw material in almost all sectors of industry. This substance is widely used, mainly as white pigment and particularly in paints, coatings, plastics, textiles, foods and feedstuffs, in paper production as well as in pharmaceutical and cosmetic products. A classification as "potentially carcinogenic to humans" would have considerable negative impacts on entire value chains.

Conclusion: The submitted proposal for classification and labelling of titanium dioxide is inappropriate from the toxicological perspective. Therefore, no classification should be made. A classification would not contribute to improving the protection of health and environment, while it would have serious and disproportionately problematic effects in almost all legal fields.

(for further details see attached documents - in English and German)

ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI.7z

Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria	Association of the Austrian Chemical Industrie	BehalfOfAnOrganisation	417
Comment received				
From toxicological perspective, the submitted proposal for classification and labelling of titanium dioxide is neither justified nor appropriate, for the following reasons.				

The proposal for classification of TiO2 is based on studies rats, which were exposed to extraordinary high doses of TiO2. It is scientifically accepted, that rats exposed chronically to high concentrations of poorly soluble particles of low cytotoxicity suffer from inflammation. The described observations in Lee, 1985, - i.e. impairment of clearance function, pulmonary inflammation and cell proliferative responses - point to a lung overload in the study. Secondary carcinogenic effects triggered by constant inflammation reaction do not qualify a substance classification as carcinogenic. Also in the study from Heinrich, 1995, an impairment of clearance function was observed, but no primary carcinogenic effects.
All relevant guidance documents by ECHA, OECD and the ECETOC Report unanimously state that results from "lung overload" studies in rats should not be transferred to humans for several reasons. In weighing the evidence of the data it needs to be pointed out that in two other inhalation studies with rats TiO2 was not carcinogenic by inhalation.

Positive results were also seen in instillation studies. However, instillation is not a physiologic route of exposure for humans; therefore positive results have also no relevance for humans.

Available human data do not suggest an association between occupational exposure to TiO2 and risk of cancer. We do not share the dossier submitter's view that there are relevant methodological limitations in these observations. Considering the several millions of yearly produced, processed and used volumes of TiO2 carcinogenic properties would have appear much earlier in the 100 year history of its commercial use.
Considering all evidence, no classification of TiO2 as "potentially carcinogenic to humans" (category 1B) / "may cause cancer by inhalation" (H350i) should be made.

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria	GL Pharma	BehalfOfAnOrganisation	418
Comment received				
The lab test results with rats are not due to TiO2 specific properties-Any dust exposure over this time limit would lead to the same results. The lung tissue was destroyed by overloading it with dust				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France	Cristal France SAS	BehalfOfAnOrganisation	419
Comment received				
Cristal is in complete agreement with the Specific Comments made in the TDMA/TDIC response to this consultation submitted on 14th July 2016.				

Dossier Submitter's Response
See response to TDMA/TDIC comment No. 99.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria		BehalfOfAnOrganisation	420
Comment received				
5- Auch in der Pharmazie, in der Kosmetik sowie als Lebensmittelzusatzstoff ist TiO2 sehr verbreitet. Es gibt keine Erkenntnisse darüber, dass dieser in der „pharmazeutischen Industrie" und als „Lebensmittelzusatzstoff" zugelassene Stoff TiO2, negative gesundheitliche Auswirkungen beim Menschen zeigt. 6- TiO2 wirkt (durch Lungenüberladung) bei Ratten krebserregen. Es ist allgemein bekannt, dass diese Erkenntnis bei Ratten, bei Menschen nicht relevant ist und zur Einstufung nicht verwendet werden soll. Das wird auch so im CLH-Report des Antragstellers festgestellt!				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		Individual	421
Comment received				
Since we use the raw TiO2 in formulation of our product we noted the absence of cancer having due to inhalation of this raw material ans this on a period of more than 30 years				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany	Verband der deutschen Lack- und Druckfarbenindustrie e. V. (VdL), the German paint and printing ink association	BehalfOfAnOrganisation	422
Comment received				
The proposed classification and labelling is not justified from the toxicological perspective.				

Titanium dioxide has been used safely for decades. There is no evidence of a carcinogenic effect in humans. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report by the applicant: "Human data do not suggest an association between occupational exposure to TiO2 and risk of cancer […] (CLH Report, page 8).

Within the REACH registration of titanium dioxide, the industry performed in 2010 a comprehensive assessment of all available scientific data: with the result that special classification and labelling of titanium dioxide is not necessary. This conclusion is reviewed regularly and adapted to the state of science. The safety of titanium dioxide is also confirmed by studies that were carried out over several decades in ca. 20,000 workers at 15 production sites, inter alia, in Germany. No negative effects on workers' health due to titanium dioxide were observed in these studies. This is reflected in statements by the employers' liability insurance association (Berufsgenossenschaft Rohstoffe und chemische Industrie - BG RC) and by the German social accident insurance (Deutsche Gesetzliche Unfallversicherung - DGUV), who have no recognized cases of occupational disease attributable to titanium dioxide.

The classification proposal in the CLH report is based on merely two studies in rats dating back to 1985 and 1995, where rats were exposed to extremely high concen-trations of titanium dioxide dust that led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and ECETOC unanimously observe that results from "lung overload" studies in rats should not be transferred to humans. It is also worth noting that comparable studies in rats did not show any carcinogenic effect for exposure by inhalation. Against this backdrop, a classification is neither justified nor appropriate from the toxicological perspective.

The carcinogenic effect found in individual animal tests is based on particle-caused inflammatory processes in the lungs due to dust exposure by inhalation. However, this is not substance-specific for titanium dioxide but characteristic of a large number of dusts (e.g. coal dust), irrespective of the underlying substance. This is also conceded in the CLH report: "Indeed TiO2 in all these combination is considered to behave in the same way as other poorly soluble low toxicity particles (e.g. coal dust, diesel exhaust particles, toner …)." [CLH Report, page 8].

Exposure by inhalation to titanium dioxide dusts can be expected primarily at the work-place. In Germany, dust exposure at the workplace is already covered by the general dust limit value (TRGS 900 / TRGS = technical rules for hazardous substances) which applies for titanium dioxide too. Furthermore, the occupational health and safety requirements for activities involving mineral dusts are concretized in the TRGS 559 "Mineral dust". Comparable rules are in place in other European countries.

So far, European law does not yet have a general dust limit value. But Directive 2004/37/EU (Cancer Directive) includes rules for the exposure to hardwood dusts which can be seen as a precedent. We propose to give up plans for classification and labelling of titanium dioxide. Instead, it would be thinkable to include activities, where workers are exposed to titanium dioxide dusts, in Annex I to the Cancer Directive and to introduce a new binding dust limit value for the handling of titanium dioxide at the workplace in Annex III.

Furthermore, we would point to the more detailed toxicological comments by the Titanium Dioxide Manufacturers Association (TDMA) and the German chemical industry association Verband der Chemischen Industrie (VCI).

ECHA note – A non confidential attachment was submitted with the comment above. VdL-Position TiO2_30.6.2016.pdf
Dossier Submitter's Response
See points 2, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99 and VCI comment No. 218.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		BehalfOfAnOrganisation	423
Comment received				
TiO2 in a non-dust form has no any risk in dermal or oral contact as also stated in the French document.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Switzerland		BehalfOfAnOrganisation	424
Comment received				
We do not support the proposed classification of TiO2 as a carcinogen category 1B, on the basis of human relevance. Inhalation of low-solubility low-toxicity particles in the rat can cause the phenomenon "lung-overload", and the CLH dossier states that the studies relevant for classification were conducted under these conditions. There is strong evidence that this is a species specific mode of action and not relevant for humans, as documented in extensive detail in the recent ECETOC Technical Report 122 - Poorly Soluble Particles / Lung Overload. The ECHA "Guidance on the application of the CLP criteria" (version 4.1, p470) acknowledges this mode of action is of questionable relevance to humans. Furthermore, epidemiology studies on TiO2 have not demonstrated a link to carcinogenicity (Ellis E.D. et al, American Journal of Industrial Medicine, 2013, 56(3), 282-291). Any proposed classification must take into account all the relevant data, and assess this against the CLP criteria.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	United Kingdom		Individual	425
Comment received				
Although several publications report the presence of TiO2 NPs apparently within cell nuclei, the possibility that these particles are either overlying the nucleus in the sections used, or were transferred from cytoplasm to nucleus during sectioning (as is considered highly likely by experts in this technique), cannot be excluded. Even in the studies of Li et				

al (2010) and Jin et al (2013), which purported to demonstrate interaction of TiO2 NPs with mouse and rat liver DNA in vivo, the possible contamination of the DNA during extraction with particles from elsewhere in the tissue, appears not to have been controlled and cannot be excluded as an explanation. Thus, there is no direct evidence of NPs binding to DNA, and all of the evidence presented indicates that, even if particles do penetrate the nucleus, oxidative damage is the only genotoxic consequence of exposure to TiO2 NPs. This is consistent with the views of other experts in nanoparticle genotoxicity, A letter from Dr Shareen Doak (University of Swansea), appended to these comments, confirms that in the many papers she and other experts have reviewed, she has never seen any direct evidence that NPs can penetrate the nucleus. Therefore, the interpretation that TiO2 might exhibit direct DNA damaging activity is speculative, and not supported by the evidence.

A detailed commentary is attached.

ECHA note – A non confidential attachment was submitted with the comment above. 020616_Commentary on CLH report for TiO2_DJK v2.doc

Dossier Submitter's Response

Seep point 3 of the attachment to the RCOM.

RAC's response

Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United States	International Paint and Printing Ink Council (IPPIC)	BehalfOfAnOrganisation	426

Comment received

IPPIC and its members also fully support the extensive work done by the TiO2 manufacturers to clarify the hazards of TiO2, including detailed analysis of the current literature and how it fails to support the proposed classification. This data, and the underlying responsible assessment, is relied on by all product manufacturers using TiO2 in order to provide for a safe and healthful workplace for manufacturing employees and downstream customers.

Evidence of "excessive toxicity", in particular studies subjecting animals to exposures at or above the MTD, are of limited utility in assigning a carcinogenic response. Such exposures give rise to cell death (necrosis) with associated regenerative hyperplasia, a process which can lead to tumor development as a secondary consequence (unrelated to the hazard of the substance itself). Furthermore, tumors in animal studies occurring only at excessive doses associated with severe toxicity generally are often doubtful for inferring carcinogenicity in humans, particularly when lower dose exposures show no corresponding effects. In addition, tumors occurring only at the site of contact (for the excessive dose as in gavage administration) need to be carefully evaluated for human relevance for carcinogenic hazard.

Finally, "hypothesized" mechanisms of tumor formation often cannot be considered relevant to humans. To be clear, where such a hypothesized mechanism is identified and relied on to advance a cancer hazard classification in the absence of corroborating human and/or animal data, then such classification is not appropriate. Only if a mode of action of tumor development is conclusively determined (i.e. not hypothesized or "proposed") as operative in humans may the carcinogenic evidence for that tumor be considered. Similarly, the existence of a secondary mechanism at prescribed dose levels (e.g. mechanisms of physiological regulation, chronic stimulation of cell proliferation) allow for a downgrading of any hazard classification.

ECHA note – A non confidential attachment was submitted with the comment above. FINAL IPPIC Comments on ECHA TiO2 Consultation 7-15-16.pdf
Dossier Submitter's Response
See points 1, 2, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		BehalfOfAnOrganisation	427
Comment received				
We have been using this substance for 39 years (since 1977) and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. In the production areas dust measurements are performed regularly. The results show that in the production areas the limit value for respirable dust particles of 1.25 mg/m³ is not exceeded. When TiO2 has been incorporated in the final product it is no more available to be inhaled." 				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		BehalfOfAnOrganisation	428
Comment received				
We have been using this substance for over 90 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Denmark	National Research Centre for the Working Environment	BehalfOfAnOrganisation	429
Comment received				
3) It is very useful that the conclusions explicitly stated that both bulk and nanoTiO2 are classified as Carc 1B 4) The literature search should cover the literature until april 2015. Here are a few studies that were published but are not included in the review that the authors may				

consider to include: Transcriptional profiling identifies physicochemical properties of nanomaterials that are determinants of the in vivo pulmonary response: 'Halappanavar S, Saber AT, Decan N, Jensen KA, Wu D, Jacobsen NR, Guo C, Rogowski J, Koponen IK, Levin M, Madsen AM, Atluri R, Snitka V, Birkedal RK, Rickerby D, Williams A, Wallin H, Yauk CL, Vogel U. Environ Mol Mutagen. 2015 Mar;56(2):245-64. doi: 10.1002/em.21936. Epub 2014 Dec 11. PMID: 25504612' and 'Pulmonary instillation of low doses of titanium dioxide nanoparticles in mice leads to particle retention and gene expression changes in the absence of inflammation. Husain M, Saber AT, Guo C, Jacobsen NR, Jensen KA, Yauk CL, Williams A, Vogel U, Wallin H, Halappanavar S. Toxicol Appl Pharmacol. 2013 Jun 15;269(3):250-62. doi: 10.1016/j.taap.2013.03.018. Epub 2013 Apr 1.PMID: 23557971'

5) Hougaard 2010 is referred in the text (page 55) but is not in the reference list.

6) Regarding the reference Saber et al, 2012 reference in the table page 124: It is stated that no positive control was included in the study. This should be corrected since CB was included as positive control.

Dossier Submitter's Response

The following abstracts are available for the studies of Halappanavar *et al*., 2015 and Husain *et al*., 2013. They were not included in the CLH report since they are not directly linked to carcinogenicity.

Halappavanar *et al*., applied transcriptional profiling to elucidate the mechanisms associated with pulmonary responses to titanium dioxide (TiO2) nanoparticles (NPs) of different sizes and surface coatings, and to determine if these responses are modified by NP size, surface area, surface modification, and embedding in paint matrices. Adult C57BL/6 mice were exposed via single intratracheal instillations to free forms of TiO2NPs (10, 20.6, or 38 nm in diameter) with different surface coatings, or TiO2NPs embedded in paint matrices. Controls were exposed to dispersion medium devoid of NPs. TiO2NPs were characterized for size, surface area, chemical impurities, and agglomeration state in the exposure medium. Pulmonary transcriptional profiles were generated using microarrays from tissues collected one and 28 d postexposure. Property-specific pathway effects were identified. Pulmonary protein levels of specific inflammatory cytokines and chemokines were confirmed by ELISA. The data were collapsed to 659 differentially expressed genes (P 0.05; fold change 1.5). Unsupervised hierarchical clustering of these genes revealed that TiO2NPs clustered mainly by postexposure timepoint followed by particle type. A pathwaybased meta-analysis showed that the combination of smaller size, large deposited surface area, and surface amidation contributes to TiO2NP gene expression response. Embedding of TiO2NP in paint dampens the overall transcriptional effects. The magnitude of the expression changes associated with pulmonary inflammation differed across all particles; however, the underlying pathway perturbations leading to inflammation were similar, suggesting a generalized mechanism-of-action for all TiO2NPs. Thus,transcriptional profiling is an effective tool to determine the property-specific biological/ toxicity responses induced by nanomaterials.

Husain, *et al*., investigated gene expression, protein synthesis, and particle retention in mouse lungs following intratracheal instillation of varying doses of nano-sized titanium dioxide (nano-TiO2). Female C57BL/6 mice were exposed to rutile nano-TiO2 via single intratracheal instillations of 18, 54, and 162µg/mouse. Mice were sampled 1, 3, and 28days post-exposure. The deposition of nano-TiO2 in the lungs was assessed using nanoscale hyperspectral microscopy. Biological responses in the pulmonary system were analyzed using DNA microarrays, pathway-specific real-time RT-PCR (qPCR), gene-specific qPCR arrays, and tissue protein ELISA. Hyperspectral mapping showed dose-dependent retention of nano-TiO2 in the lungs up to 28days post-instillation. DNA microarray analysis revealed approximately 3000 genes that were altered across all treatment groups (±1.3 fold; $p<0.1$). Several inflammatory mediators changed in a dose-

and time-dependent manner at both the mRNA and protein level. Although no influx of neutrophils was detected at the low dose, changes in the expression of several genes and proteins associated with inflammation were observed. Resolving inflammation at the medium dose, and lack of neutrophil influx in the lung fluid at the low dose, were associated with down-regulation of genes involved in ion homeostasis and muscle regulation. Our gene expression results imply that retention of nano-TiO2 in the absence of inflammation over time may potentially perturb calcium and ion homeostasis, and affect smooth muscle activities.

Hougaard *et al*.
The reference of the study is the following: Hougaard KS, Jackson P, Jensen KA, Sloth JJ, Löschner K, Larsen EH, Birkedal RK, Vibenholt A, Boisen AM, Wallin H, Vogel U.Effects of prenatal exposure to surface-coated nanosized titanium dioxide (UV-Titan). A study in mice.Part Fibre Toxicol. 2010 Jun 14;7:16. doi: 10.1186/1743-8977-7-16. Erratum in: Part Fibre Toxicol. 2011;8:14.

Saber *et al*.
We agree that, in this study, carbon black was used as positive control.

RAC's response

Noted. The data cannot be directly used for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
10.07.2016	United Kingdom	Zircon Industry Association (ZIA)	BehalfOfAnOrganisation	430

Comment received

1. Regarding the conclusions on carcinogenicity for the oral route: Page 47: 'In conclusion, no carcinogenic concern has been identified after oral exposure to TiO2. Oral uptake of TiO2 seems to be rather limited even if it cannot be excluded that some forms of TiO2 could be better absorbed, in particular with specific coating and/or size. Considering the presented carcinogenic mode of action (see paragraph Carcinogenic mode of action) of TiO2 requiring a sufficient accumulation of particles, the low absorption of different forms of TiO2 reported in various kinetics studies might explain the negative carcinogenic outcome in the 2 studies available.' This statement assumes that TiO2 is carcinogenic if it gets into cells, however there is no evidence for this and ignores the fact that the Mode of Action is a secondary effect of a specific inhalation response. In addition on page 47 it is stated 'From these studies, the overall conclusion is that TiO2 is not carcinogenic by the oral route although no firm conclusion can be reached about the possible carcinogenicity of this compound to Fischer 344 based on an increase of adenoma/adenocarcinomas of the thyroid according to one reviewer of the NCI (1979) study. However, it should be noted that the doses were very high, often higher than that is recommended in the OECD guideline.' The overriding conclusion from the NCI study was that the thyroid tumours were not considered to be related to the administration of the test chemical, hence the conclusion should be that TiO2 is not carcinogenic by the oral route and not cast doubt based on one individual reviewer. Based on all the data presented there is nothing to indicate that it could be directly carcinogenic at all.

2. Regarding the dermal route there is no evidence of carcinogenicity however, again, the authors assume that TiO2 is carcinogenic and ignore the fact that the mode of action is a secondary effect of a specific inhalation response Page 48 'In conclusion, no carcinogenic concern has been identified after dermal exposure to TiO2. Dermal penetration of TiO2 seems to be rather limited even if it cannot be excluded that some forms of TiO2 could be better absorbed, in particular with specific coating and/or size.

Considering the presented carcinogenic mode of action of TiO2 (see paragraph Carcinogenic mode of action) requiring a sufficient accumulation of particles, the low absorption might explain the lack of systemic carcinogenic effect reported in the available studies.'

3. Regarding the inhalation route there is no argument that tumours are seen at a high dose in rats (conclusion Page 50). However it is not noted by the authors that the tumour findings in the rat was at an excessive unacceptable doses since the clearance rates exceed the 1 year limit suggested on OECD 116 (page 71). In addition, the CLP Regulation Annex I: 3.6.2.2.6. lists 'Some important factors which may be taken into consideration, when assessing the overall level of concern ..' which includes (j) the possibility of a confounding effect of excessive toxicity at test dose and the CLP guidance (referring to Annex I: 3.6.2.2.6 (j)) notes 'Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard'. Here the automatic assumption that this is relevant for humans should not be made at the very least due to the effects being only at the site of contact and at excessive doses, but should be considered alongside the other information further discussed.

4. In the arguments that the effects in rats lead to Category 1 and in the consideration of other species, it is suggested that the lack of effects in other species could lead to an underestimation of carcinogenicity - Page 68: 'TiO2 was not proposed to be placed in Category 2 since malignant ant tumours were reported in more than one experiment of adequate quality. These malignant findings are only found in rats, the unique tested species. It is also recognised that other rodent species would be less sensitive for the hypothesized mode of action leading to an underestimation of carcinogenicity.' This ignores the fact that one study was by intratrachael instillation which does not reflect the deposition that would occur by inhalation and therefore not relevant for this mode of action. It also ignores the fact that the lack of effects on other species supports the mode of action of poorly soluble particles being a rat specific mechanism due to differences in physiology etc. It does not lead to an underestimation of carcinogenicity. Higher testing doses cannot be used as this would cause unnecessary suffering as indicated in the OECD Guidelines (451 and 116) which discourages inhalation of doses that overwhelm pulmonary clearance which lead to tissue responses that are specific to the species being tested and hence limit the top dose. As already noted the high dose in the rat study was excessively high. The document also states on, Page 61. 'Finally, although no lung tumour was found in mice and hamsters, they are known to give false negatives to a greater extent than rats in bioassays for some particulates that have been classified by IARC as human carcinogens (limited or sufficient evidence), including crystalline silica and nickel subsulfide. The lung tumour response to other known human particulate carcinogens (such as tobacco smoke, asbestos, diesel exhaust…) is significantly less in mice than in rats. Therefore, the risk of several known human particulate carcinogens would be underestimated by using dose response data & hazard properties from rodent models other than rats.' Comparison of the effects of an inert poorly soluble substance such as titanium dioxide to crystalline silica and nickel subsulfide, or indeed tobacco smoke, asbestos or diesel exhaust, is not relevant as each of these substances are likely to act via a different mechanism than by pulmonary overload, although each may act through a secondary mechanism.

2. Specific Comments on Mode of Action
a. While the authors seem to accept, in several places, that the carcinogenic mode of

action of TiO2 in rats seems to be due inflammatory process and oxidative stress due to the biopersistence and solubility (PSP) (e.g. Pages 8, 58, 63, 68), hence an overload mechanism rather than a direct effect by TiO2, there is a continual push to argue against this and it fails to reference key reviews on this widely accepted concept such as the recent thorough review of the literature by ECETOC in 2013 (Technical Report No. 122, Poorly Soluble Particle/Lung Overload). The authors also dismiss information such as from NIOSH (2011) which concluded that TiO2 is not a direct-acting carcinogen, but acts through a secondary genotoxicity mechanism. NIOSH is referred to in several places P59, and P65, but on P 61 the authors state that 'The relevance of rat model predicting human response to inhaled particles is the subject of controversial discussion. A comparison of lung tumor types in rats and humans and the relevance of rat model in risk assessment are well described by the NIOSH (2011)' implying that NIOSH had made this conclusion. It should be noted that NIOSH concluded 'that there are insufficient data at this time to classify fine TiO2 as a potential occupational carcinogen since the tumorigenic dose (250 mg/m3) was significantly higher than currently accepted inhalation toxicology practice'. This supports the notion that the top dose in the rat inhalation study was excessive
b. In addition, the relevance of this mode of action for TiO2 and a possible direct effect of genotoxic mechanism for TiO2 is suggested based on unsupportable evidence as indicated on P59: ' In addition, some accumulation of particles in nucleus cells was reported in few publications. Thus, even if the presence of particles in the nucleus, with quantitative data, are rarely evaluated in the publication, a primary genotoxic mechanism by direct particle interaction with DNA cannot be totally ruled out'.
The overriding data on the genotoxic effects is negative and based on weight of evidence this should be a categoric statement if following the CLP Regulation (Annex I: 3.5.2.3.9. The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1)). The mere presence of particles does not indicate a genotoxic mechanism, it is hard to see how particles would get into the nucleus in vivo via the normal routes of exposure and knowing that small particles agglomerate, but more importantly there is evidence that there are methodology issues in the types of studies that supposedly see particles in the nucleus and this could be an artefact of the methodology – see Hondow et al., 2010, Nanotoxicology, 2010; 1–13; STEM mode in the SEM: A practical tool for nanotoxicology. Hence this cannot be used to indicate a possible primary genotoxic mechanism.

3. The CLP Regulation Annex I: 3.6.2.2.6. Lists 'Some important factors which may be taken into consideration, when assessing the overall level of concern..' which includes (k)) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. This is pertinent to much of the document, and is key in that the mode of action is not to be relevant for humans and hence does not support classification.

4. It is noted on page 8-9 that other substances are recognised as operating via a similar mode of action 'The proposed mechanism is already described for other substances such as aluminium oxide, insoluble nickel salts and iron oxides, acting as poorly soluble low toxicity particles, which elicit lung tumors in rats following prolonged exposure at sufficiently high concentrations.' There has been a recently published peer review of all of the literature on Iron Oxides indicating the data that supports this mode of action that is specific to rats (http://www.ncbi.nlm.nih.gov/pubmed/26863929).

Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Austria		Individual	431
Comment received				
About the studies referenced by the politicians (which are also referenced in the pdf proposal at the above link): They use so called Lung Overload Tests. What does that mean? Rats (sometimes mice) had to inhale large amounts of TiO2 dust. That caused alterations in the lung tissue. This is the basis for their claim that it is cancerous. However, ALL KINDS of dust inhaled into the lungs have this effect. If you inhale tons of sawdust, for example, that can also lead to alterations. People have worked with TiO2 in various industries for decades. There are tons of studies that show no correlation between TiO2 and cancer in real life.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece		BehalfOfAnOrganisation	432
Comment received				
3. There aren't of cases of cancer in our workforce caused by inhalation of TiO2 during the manufacture of coatings, over a long period of time (e.g. since 1948, the last 60 years); ECHA note – A non confidential attachment was submitted with the comment above. 2016-07-15 Public Consultation particip. (confidential) comm.pdf				
Dossier Submitter's Response				
See points 1, 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Jänecke+Schneemann Druckfarben GmbH	BehalfOfAnOrganisation	433
Comment received				
Titandioxid wird seit mehr als 60 Jahren bei uns in der Produktion von Druckfarben verwendet. Ein Zusammenhang zwischen der Verwendung von Titandioxid und Krebserkrankungen der Mitarbeiter ist uns nicht bekannt. Bei der Handhabung von Titandioxid in Pulverform wird entsprechende persönliche Schutzausrüstung zusätzlich zu Arbeitsschutzmaßnahmen wie z. B. geeignete Absaugung eingesetzt. Sobald das Titandioxid in unsere Produkte (Druckfarben) eingearbeitet ist, kann es nicht mehr eingeatmet werden, da kein Staub mehr vorliegt.				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany	BASF SE	BehalfOfAnOrganisation	434
Comment received				
The dossier submitter proposes to classify Titanium dioxide as a carcinogen for the inhalatory route based on experimental findings in rats which occurred under lung overload conditions and are described to be a generic response of inert particles. The underlying mechanism, specifically in relation to human relevance, has been discussed in depth in the ECETOC Technical Report no. 122 on poorly soluble particles/lung overload published in 2014. The conclusion on the human relevance differs significantly from the assessment by the dossier submitter in that there are strong arguments against the simple transfer of the rat findings to humans. No reference is made to this report in the CLH dossier which is unfortunate since it is the result of intensive discussions among global experts in the field of inhalation toxicology. The CLH report proposes to classify the substance in category 1B (inhalation) because "…it appears that lung retention and chronic pulmonary inflammation in humans are consistent with the findings in rats". No reference is given for this assumption. Arguments arising from data on Titanium dioxide and poorly soluble substances in general are mixed. In contrast, as described in detail in the ECETOC report no 122, the response by rats to chronic inert particle exposure is considerable different than that of other species. This is reflected in the ECHA guidance on information requirements and chemical safety assessment of 2012 (Appendix R8-15) which states that "The relevance of lung overload in animals to humans is currently not clear and is subject to continuous scientific debate". Most importantly, epidemiology studies did not show a link between Titanium dioxide dust exposure and lung cancer in workers. The epidemiology data were also used for the IARC report (2010) which concluded that there is inadequate evidence for carcinogenicity in humans. Since then, two publications on occupational exposure and mortalities at titanium dioxide production facilities supported the absence of a carcinogenic potential for humans (Ellis ED et al. J Occup Environ Med. 2010 Mar;52(3):303-9; Ellis ED et al. Am J Ind Med. 2013 Mar;56(3):282-91). BASF considers that the classification in Category 1B (inhalation) is not justified. In the CLH report, the comparison between criteria in section 3.6.2 of the CLP directive and the available data is not conclusive. Requirements on the strength of evidence regarding human relevance are not clearly depicted and the evidence against human relevance is not adequately taken into account. It is expected that a re-assessment according to the CLP criteria would generate additional clarification. BASF therefore recommends to reject this proposal.				
Dossier Submitter's Response				
See points 2 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece	HELLENIC ASSOCIATION OF CHEMICAL INDUSTRIS	BehalfOfAnOrganisation	435
Comment received				
From the toxicological perspective, a classification of titanium dioxide as potentially carcinogenic is neither necessary nor justified (see specific comments below). Given the automatic link to regulatory requirements, such a classification would have serious negative effects on the market for paints, coatings and printing inks without contributing				

to the protection of health and the environment. The risks under discussion are based solely on dust exposure by inhalation. But this is not substance-specific for titanium dioxide; it is characteristic of a large number of dusts. Against this backdrop, we propose to give up plans for a classification and labelling of titanium dioxide. Instead, a new binding dust limit value could be introduced for the handling of titanium dioxide at the workplace.

At present, substances are classified at EU level exclusively on the basis of their intrinsic properties. The real risk in the use of a substance is not examined. Because of the automatic linking to classification in many legal provisions on occupational health and safety and consumer and environmental protection, this approach can lead to excessive and unintended restrictions. The given case of titanium dioxide is an example of this. For this reason, we are advocating in favour of additional risk and impact assessments to be performed in future for all substances as soon as a harmonised classification is proposed.
The proposed classification and labelling is not justified from the toxicological perspective. Titanium dioxide has been used safely for decades. There is no evidence of a carcinogenic effect in humans. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report by the applicant: "Human data do not suggest an association between occupational exposure to TiO2 and risk of cancer […] (CLH Report, page 8).
Within the REACH registration of titanium dioxide, the industry performed in 2010 a comprehensive assessment of all available scientific data: with the result that special classification and labelling of titanium dioxide is not necessary. This conclusion is reviewed regularly and adapted to the state of science.
The classification proposal in the CLH report is based on merely two studies in rats dating back to 1985 and 1995, where rats were exposed to extremely high concen-trations of titanium dioxide dust that led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and ECETOC unanimously observe that results from "lung overload" studies in rats should not be transferred to humans. It is also worth noting that comparable studies in rats did not show any carcinogenic effect for exposure by inhalation.

Dossier Submitter's Response
See points 2 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France		BehalfOfAnOrganisation	436

Comment received

We believe TiO2 does not have carcinogenic potential on humans from following reasons.
Among epidemiological studies including epidemiological cohort studies and population based case control studies, none of them was identified to prove the clear correlation between the occupational exposure to titanium dioxide and carcinogenicity in the respiratory organ.
The causal relation of the carcinogenicity associated with titanium dioxide has not been reported since titanium dioxide has placed in the market for more than 90 years.
In this context, we believe the environmental condition exposed on human life is not comparable to that of animal testing conditions.
According to two inhalation studies in rat, increases of bronchioalveolar adenoma, benign keratinizing cystic squamous cell tumours, and adenocarcinoma were observed only in female rats, whilst it was not recognized that the increase of carcinogenesis or the

increase of mortality in other two studies in rats or a study in mice. In addition, two inhalation studies in rat mentioned above, the study exposed rats to titanium dioxide at concentrations of 0, 10, 50, 250 mg/m3 showed that the maximum dosage caused bronchioalveolar adenoma, and it suggested overloading context (Lee, 1985 R2). It's known that pulmonary responses to inhaled particles of TiO2 differ by species, we consider that it's inappropriate to extrapolate the result of carcinogenesis in rat studies directly to humans. We also need to discuss "Impact of the coating". The current proposal concluded TiO2 as Carc. Cat 1B-H350i, regardless of the morphology or the crystal phase or the surface treatment of the substance. In the section of "Impact of the coating" (from page 53), it is considered that the surface treatment is one of the most influential factors among all other physical and chemical characteristics of the substance in terms of carcinogenicity due to a number of reports suggesting different surface treatments impacting on the production of reactive oxygen species or the induction of inflammatory responses. However, the conclusion in this section is that coating is not a parameter to consider for classification, since it's impossible to distinguish which coating, if any, will induce responses. We believe that the further study shall be needed for the classification of TiO2 Carc. Cat 1B-H350i to be concluded considering the impact socioeconomically although we respect the position that suspicious levels of a substance should be restricted.
Dossier Submitter's Response
See points 1 and 2 of the attachment to the RCOM. Please note that data were considered sufficient for the classification proposal for carcinogenicity.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Greece	HELLENIC COATING ASSOTIATION	BehalfOfAnOrganisation	437
Comment received				
The proposed classification and labelling is not justified from the toxicological perspective. Titanium dioxide has been used safely for decades. There is no evidence of a carcinogenic effect in humans. In epidemiological studies no connection was found between exposure at the workplace and a cancer risk. This is also noted in the CLH report by the applicant: "Human data do not suggest an association between occupational exposure to TiO2 and risk of cancer […] (CLH Report, page 8). The classification proposal in the CLH report is based on merely two studies in rats dating back to 1985 and 1995, where rats were exposed to extremely high concen-trations of titanium dioxide dust that led to so-called "lung overload" effects. However, all relevant guidance documents by ECHA, OECD and ECETOC unanimously observe that results from "lung overload" studies in rats should not be transferred to humans. It is also worth noting that comparable studies in rats did not show any carcinogenic effect for exposure by inhalation.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. RAC thoroughly discussed the reliability of data for classification purposes.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Norway	Jotun A/S	BehalfOfAnOrganisation	438
Comment received				
Jotun A/S supports the comments made by the Titanium Dioxide Manufacturers Association/Titanium Dioxide Industry consortium and the German Chemical Industry Association (VCI). ECHA note – A non confidential attachment was submitted with the comment above. Consequence of a TiO2 Ban.docx				
Dossier Submitter's Response				
See response to VCI comment No. 218 and point 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	FCIO - BG Lack- und Anstrichindustrie	BehalfOfAnOrganisation	439
Comment received				
Bisher haben wir keine wie auch immer gearteten gesundheitlichen Probleme während der Manipulation auf unserem Lager und in der Logistik festgestellt. Auch von unseren Kunden sind uns keine derartigen gesundheitlichen Probleme bekannt.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Greece	NEOKEM S.A.	BehalfOfAnOrganisation	440
Comment received				
Our company currently employs 85 people. We have been using this substance for more than 40 years. As we successfully manage the workplace exposures of dust , we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. In any case our workers always use the appropriate masks for dusts as we generally consider the handling of any dust as a dust hazard material.				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Sweden		BehalfOfAnOrganisation	441
Comment received				
We have used TiO2 in powder form for more then 55 years in our dayly work. Many of our employees has had dayly exposure for more than 25 years and we have never had any				

signs of cancer diseases.
Dossier Submitter's Response
See point 2 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	WUK	BehalfOfAnOrganisation	442
Comment received				
No evidence of any such effect on our workers over last 45+ years. We monitor health of our workers with yearly medicals.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	HMG paints	BehalfOfAnOrganisation	443
Comment received				
We have recorded no linkage between Titanium dioxide usage and cancer within our workforce. Sun Chemical Europe				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria	Treibacher Industrie AG	BehalfOfAnOrganisation	444
Comment received				
We support the scientific comments, arguments and statements provided by TDMA and TDIC.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		MemberState	445

Comment received

The experimental data provide clear evidence of a carcinogenic effect of TiO2 in the lungs. Two positive carcinogenicity studies in rats and supporting evidence from instillation studies are in general compliant with the criteria for a classification as Carcinogen 1B.

Arguments could be raised which could question the classification as Carcinogen Cat. 1B to favour a Carcinogen Cat. 2 classification. These points are already covered to a major extent in the CLH proposal. Nevertheless, it would strengthen the proposal in summarizing these points in the justification for the classification for carcinogenicity in chapter 2.2 Short summary of the scientific justification for the CLH proposal, Carcinogenicity:

The following arguments could be raised which could question the classification as Carcinogen Cat. 1B to favour a Carcinogen Cat. 2 classification:

i) Rat lung tumours are found in the overload condition only. Thus, there is a threshold-like action of titanium dioxide favouring a Carc. Cat. 2 classification.

ii) The rat is overly sensitive to overload-dependent inflammation. Lung carcinogenicity is the consequence of overload only in rat. Hamster, mice, and monkeys do not develop lung tumours after chronic inhalation of granular biodurable particles.

The arguments can be discussed as follows:

response to i)
A clear-cut threshold for overload cannot be derived as particle clearance from the lung decreases in a linear fashion with increasing dust load also below the Morrow threshold of overload (Morrow PE. Fundam Appl Toxicol. 1988 10(3):369-84; Roller M (2003) Eur J Oncol 8(4), 277-293). Thus, there is no established consensus in the scientific community that titanium dioxide is a threshold carcinogen.

response to ii)
Lung carcinogenicity by titanium dioxide is a consequence of chronic inflammation which was assumed by some researchers to be species-specific for the rat as hamsters and mice did not show lung tumors after granular biodurable particle exposure. Counterarguments are that the latter species may not be adequate indicators for human lung carcinogenicity. For instance, benzoapyrene and vinyl chloride were negative after inhalation in hamsters and mice were negative after crystalline silica exposure, respectively. Moreover, hamsters and mice were studied more rarely for lung carcinogenicity of particles. The negative monkey data after granular biodurable particle can be explained by the fact that only few animals were studied and only one dose was used for only 2 years.

It is agreed that inhalation is the only route that is relevant for classification. Based on the data available and taking into account the specific mode of action in the respiratory system it is considered to be unlikely that other routes would lead to a carcinogenic response.

Other non-physiological routes (such as intratracheal application) may mimic worst case exposure conditions and effects after single/repeated peak exposure(s). It is agreed that

these studies may give supporting evidence, but do not allow to conclude on dose-responsiveness after long-term inhalation.

Some specific comments:
p. 18:
The citation Roller 2005 should be checked (Mohr et al., 2005?)

p.35:
It should be considered to shift the intratracheal instillation studies from the inhalation section to "other routes"

p. 46:
The observation of the higher potency of nano-TiO2 compared to the bulk (pigment) requires further investigation, which is reflected by the ongoing debate in terms of the relevant dose metric (other measures besides surface are, particle void volume or particle number).

Dossier Submitter's Response

See points 1 and 2 of the attachment to the RCOM.

Intratracheal instillation studies:
We agree, nevertheless, the CLH report will not be modified at this stage of the process.

Citation of Roller *et al.*, 2005 :

The reference is the following : Pott F, Roller M. Carcinogenicity study with nineteen granular dusts in rats. Eur J Oncol. 2005; 10(4):249–81.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Germany	EWIMA: European Writing Instruments Manufacturers Association	BehalfOfAnOrganisation	446

Comment received

The essential criteria for the classification of TiO2 as a carcinogen (Carc. Cat 1B, H350i) are not fulfilled:
• The evidence indicated in the CLH proposal originate from animal experiments without conclusiveness, as the results are contradictory to present epidemiological studies.
Rats suffering from lung cancer after their lungs have been treated with an overdose of TiO2 ("overload context"). Since it is known that rats and humans often react very differently to chemical substances, a carcinogenic effect of TiO2 on humans cannot be concluded from these debatable results.

• The epidemiological studies mentioned in the CLH report are of much more significance. The health status of thousands of workers of TiO2 production plants have been observed over years. The data do not indicate a correlation between the level of the TiO2 exposition and the frequency of workers suffering from lung cancer.
The results of the epidemiological studies presented by ANSES verify the experiences of manufacturers of writing instruments and similar products concerning TiO2.

For decades, the white pigment has been used in huge amounts as an ingredient for colored leads, pastels and lacquers.
A conspicuous increased frequency of lung cancer diseases has never been observed in the writing instruments industry, although in former times the employment protection measures were of a low level.
Nowadays workers are protected from all types of dust by exhaust fans. In this context the supposed health hazard properties of TiO2 seem to be of no relevance.
Pigment dispersions including TiO2 are often used for liquid formulations in the writing instruments industry and thus workers are not exposed to TiO2 respirable particles.

• In addition, a health risk is not expected from finished products, including writing instruments, where the pigment is bound in a matrix.

We are convinced that consumer products containing TiO2 are safe and do not bear a health risk which originates from the pigment.

The proposed classification of TiO2 as carcinogenic is scientifically not justified and thus has to be dismissed.
Epidemiologic studies supporting the proposal do not exist. The animal experiments show a carcinogenic effect in rats, but they are of low evidence. A carcinogenic effect in humans cannot be concluded from these results. In fact, the lots of existing epidemiologic studies proof that TiO2 is harmless to humans.

For a profund discussion in detail on the data and on the conclusion described in the CLH report, we would like to refer additionally to the contribution of TDMA to the current public consultation.

Dossier Submitter's Response

See points 1, 2 and 4 of attachment to the RCOM and reponse to TDMA/TDIC comment No. 99.

RAC's response

Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2016	Germany	Geholit+Wiemer Lack- und Kunststoff-Chemie GmbH	BehalfOfAnOrganisation	447

Comment received

We have been using this substance for as long as our company exists, which is more than 125 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers.
When handling TiO2 in powder form or when handling any powders at all our workers are protected by local exhaust ventilation or by wearing appropriate dust masks. All controls of the strict German occupational exposure limits in the past years show the reliablibity and effectiveness of these risk mitigation measures.
During production all powders are well mixed into and entirely wrapped by binders. After incorporation in our products TiO2 is bound and no longer inhalable. Therefore no specific risks evolve from TiO2 and its specific chemical or physical properties for the users of our products.
According to REACH a classification as carcinogen would oblige industry to substitute TiO2 with materials not yet identified, not as well examined, or already banned by industry due

to negative properties. There is to date no known alternative in regard to low toxicity or high functionality of TiO2.
Dossier Submitter's Response
See points 2, 4 and 5 of attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Owens Corning Veil Netherlands B.V.	BehalfOfAnOrganisation	448
Comment received				
We fully support the scientific position provided by TDMA/TDIC for no classification of TiO2.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment no. 99.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	ACTEGA Terra GmbH	BehalfOfAnOrganisation	449
Comment received				
We have been using this substance for more than 20 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	450
Comment received				
We successfully keep the workplace free of dust (we use efficient ventilation and extraction and other risk management measures). We are not aware of any connection between the use of TiO2 and the development of cancer (no cases of cancer in our company caused by the inhalation of TiO2 during the manufacturing of coatings over the past 30 years).				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	451
Comment received				
We successfully keep the workplace free of dust (we use efficient ventilation and extraction and other risk management measures). We are not aware of any connection between the use of TiO2 and the development of cancer (no cases of cancer in our company caused by the inhalation of TiO2 during the manufacturing of coatings over the past 30 years).				
Dossier Submitter's Response				
See points 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany		BehalfOfAnOrganisation	452
Comment received				
Furthermore, neither our Health and Safety Executive nor our company doctor have ever detected any problems with those employees working with TiO2 in powder form over the past 20 years. This has been checked on a regular basis.				
Dossier Submitter's Response				
See point 2 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	FeRFA - The Resin Flooring Association	BehalfOfAnOrganisation	453
Comment received				
Please refer to VCI statement ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI Statement TiO2 English.pdf				
Dossier Submitter's Response				
See response to VCI comment no. 218.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Dane Color UK Ltd.	BehalfOfAnOrganisation	454
Comment received				
No evidence from worker records ECHA note – A non confidential attachment was submitted with the comment above.				

TDMA response 2016-07-06.docx
Dossier Submitter's Response
See points 2, 4 and 5 of attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	KRONOS INTERNATIONAL, Inc.	BehalfOfAnOrganisation	455
Comment received				
KRONOS is a member of several national and international associations such as VCI and VdMI in Germany, TDSC in the US, and TDMA and TDIC in Europe. As member of these associations, KRONOS was involved in the compilation of the scientific comments addressing the specific endpoints, especially the one of TDMA and TDIC. We therefore refrain from posting these comments but refer instead to the input given to this consultation by the named associations.				
Dossier Submitter's Response				
See response to TDMA/TDIC comment No. 99 and to VCI comment No. 218.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Germany	Krahn Chemie GmbH	BehalfOfAnOrganisation	456
Comment received				
We have been supplying this substance for more than 15 years and we are not aware of any relation between the use of TiO2 and the development of cancer by workers of any of our customers. When handling TiO2 in powder form or when handling any powder to our knowledge their workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled."				
Dossier Submitter's Response				
See points 1, 2 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Albemarle Europe SPRL	BehalfOfAnOrganisation	457
Comment received				
Summary section 2.2 page 8, Section 4.1.2 pages 38 to 41, Section 4.1.5 pages 66-69 comparison with criteria The CLH report states on page 8 ""Human data do not suggest an association between occupational exposure to TiO2 and risk for cancer. However, all these studies have methodological limitations and the level of exposure reported is debatable." We are very surprised about this statement understating the human evidence, as titanium dioxide has				

a particularly good epidemiological data base available.

The review of the human information in chapter 4.1.2 is very brief and does not contain an in depth analysis of the extant epidemiology studies. Furthermore, one important study in titanium dioxide manufacturing workers was not quoted at all (Ellis et al., 2010: Mortality among titanium dioxide workers at three DuPont plants. J. Occup. Environ. Med. 52(3): 303-309; Ellis et al., 2013, Occupational exposure and mortality among workers at three titanium dioxide plants. Am J. Ind. Med. 56: 282-291). The human epidemiology data base is important for the overall evaluation and also supports the evidence that effects observed in rats under overload conditions are not relevant for the human situation.

Summary section 2.2 pages 8 and 9 and chapter 4.1 Carcinogenicity (page 16 to 37)The classification proposal is based essentially on only one inhalation carcinogenicity study in rats (Lee et al., 1985) that showed an increase in lung tumour incidence in rats only at dose levels that clearly exceeded the maximum tolerated dose level and was obtained under overload conditions. This was also concluded by NIOSH, 2010 (NIOSH Current Intelligence Bulletin 63 – occupational Exposure to Titanium Dioxide NIOSH Dept. of Health and Human Services, 2010) who stated that the 250 mg/m3 concentration in this study was an excessive dose and is not relevant for human risk assessment. Although the summary claims the proposal is based on two inhalation studies, the second study that reported an increased incidence of lung tumours in female rats has been rated as reliability 3 in the table on page 17 and has several shortcomings (titanium dioxide exposure was only a satellite group of another study; only one sex was used; no dose response was studied; the exposure duration was unusual: 18 h/day, 5d/week for 24 months; and the pathological characterization of the tumours is not in accordance with more recent international agreements). Furthermore, two instillation studies are used as supporting evidence (only one of them had a reliability rating of 2 on page 17). We regard this as highly questionable as in those studies a very high dose is administered in a single installation while similar accumulation in the lung by inhalation will only occur over a prolonged time and the dose rate is important for the effect. While those studies can be used in research to compare certain reactions, they should not be used for a hazard assessment following repeated inhalation exposure. In contrast, other studies, for example the inhalation study of Muhle et al. 1989 were disregarded (p.49) due to inter alia, lower concentrations used, while these concentrations although still rather high were more realistic than the concentrations in the Lee et al. 1985 study.

The CLH report states on page 8: ..” the overload concept is relevant for humans, and in particular for workers exposed to high dust concentrations.”

There is no justification given for this conclusion and no attempt is made to relate the concentrations that led to the findings in rats to human equivalent concentrations.

The assumption that carcinogenicity in rats following lung overload is relevant for human hazard assessment, is in contrast to the current scientific state of the art. For example, the Guidance document No. 116 of the Organisation for Economic Co-operation and Development (OECD) (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)47&doclanguage=en) on the carrying out of carcinogenicity studies states:
“3.2.3 The inhalation route of exposure
135. For substances likely to accumulate in the lung over time due to poor solubility or other properties, the degree of lung-overload and delay in clearance needs to be estimated based on adequately designed pre-studies; ideally a 90-day study with post-exposure periods long enough to encompass at least one elimination half-time. The use of

concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged."
The high dose in the key study used for the classification proposal (Lee et al., 1985) would definitely fall into the "discouraged " exposure levels.
In the ECHA Guidance Document on CLP (https://echa.europa.eu/documents/10162/13562/clp_en.pd), the "lung overload" is expressly mentioned as a mechanism of unclear relevance for humans, so that it should not be used for classification:
"3.9.2.5.3. Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))
In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans. Examples for such species differences are described in this section.
[…]
Lung Overload
The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate."
[ECHA Guidance document, page 469/470].
To this end ECETOC, TR 122, Poorly Soluble Particles / Lung Overload , 2014 has reviewed the current state of the scientific debate on the relevance of rat tumour response to human hazard assessment. This review led to the following conclusions:
""The synopsis of currently available scientific data on 'lung overload' allows the Task Force to conclude that:
• The rat represents a particularly sensitive model concerning the development of pulmonary non-neoplastic lesions and, moreover, a unique model with regard to lung neoplastic responses under conditions of lung overload.
• Lung tumours have to be regarded as the final phenotypic `adverse outcome` only in rats, whereas in other species non-neoplastic lesions seem to be the respective `adverse outcome`.
• Humans are less sensitive to `lung overload` as epidemiological studies thus far have not been able to detect an association between occupational exposures to poorly soluble particles of low toxicity and an increased risk for lung cancer.
• The divergence in the largely common mechanistic sequence of the adverse outcome pathway may be related to the biological diversity of detoxification systems, especially in species specific antioxidant defence resulting in a more pro-inflammatory environment in rats compared to a more anti-inflammatory environment in other rodent species.
• The measured difference in particle retention, distribution and clearance patterns in the lungs of exposed rats versus primates or humans may account for both the greater sensitivity in rats and corresponding differences in pulmonary pathological responses to long term particle exposures.
• Sight differences in the bio solubility of deposited poorly soluble particles in biological fluids may influence chemical dissolution and based hereupon accelerate or slow down the process of lung overload development.
• Independent of particle size, inhalation exposure to high concentrations of low soluble particles of low toxicity are eliciting comparable localized pulmonary toxicity via processes that are pro-inflammatory in nature, causing oxidative stress and an persistent pulmonary inflammatory response.
• The mechanisms leading to an oxidative and inflammatory pulmonary status are clearly threshold related.
• There is no "nano-particle specific lung overload toxicity" and mechanistic findings for conventional "micro" particles apply also for nano-structured particles."
With regard to the relevance for humans ECETOC, 2014 (chapter 5.7 Relevance of lung

overload for humans) concludes: "Therefore, it was noted that the findings in rats are not useful endpoints for human risk evaluations of poorly soluble particulate exposures. In contrast to the experience with rats, epidemiological findings in coal mine workers, a -well studied occupationally- exposed group of workers with routine "particle overload" in their lungs, clearly demonstrate a lack of lung cancer risk when correlated with exposures. In addition, results from several extensive human epidemiology studies in titanium dioxide or carbon black exposed workers clearly have demonstrated that long-term occupational exposures to these particle-types do not cause lung cancer or non-cancerous diseases of the respiratory tract." With regard to considerations for classification ECETOC, 2014 (chapter 8.5.1 Classification for tumorigenic and non-tumorigenic effects) concludes on the relevance for carcinogenicity classification: "Based on the information provided in this report, one can conclude that lung overload in its distinct form and with all its consequences is a rat specific phenomenon. Rat inhalation studies with poorly soluble particles in which lung overload has been observed have therefore no human relevance with regard to any observed tumourigenic effects and, without appropriately considering the dose-response differences between rats and humans, of little human relevance for non-tumourigenic effects." In conclusion we would expect a more thorough weight- of- evidence approach considering all available data and the dosimetric aspects and are convinced that this would lead to a non-classification conclusion for titanium dioxide from a toxicological point of view.
Dossier Submitter's Response
See point 2 of attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Huntsman Pigments and Additives	BehalfOfAnOrganisation	458
Comment received				
Huntsman fully endorses the scientific data and comments submitted by the TDMA and TDIC on behalf of the industry. No classification can be justified for mutagenicity.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Firwood Paints Ltd	BehalfOfAnOrganisation	459
Comment received				
We have no record of cases of mutagenicity that have been caused by our use of titanium dioxide or other powders handled in our production process.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	FeRFA - The Resin Flooring Association	BehalfOfAnOrganisation	460
Comment received				
Please refer to VCI statement ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI Statement TiO2 English.pdf				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to VCI comment No. 218.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Dane Color UK Ltd.	BehalfOfAnOrganisation	461
Comment received				
No evidence from worker records ECHA note – A non confidential attachment was submitted with the comment above. TDMA response 2016-07-06.docx				
Dossier Submitter's Response				
See point 1, 3, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium	Albemarle Europe SPRL	BehalfOfAnOrganisation	462
Comment received				
Section 2.2 Short summary page 8/9 , Section 4.1.3 Summary of carcinogenicity studies, p. 59 genotoxicity. The statement on page 8: "However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO2 was found in the cell nucleus in various in vitro and in vivo studies" is speculative and not supported by a sound analysis of the respective studies. A simple "finding" in a study can well be an experimental artefact if not substantiated by sound analytical data and it should be accompanied by evidence of DNA damage. As we understand it, there is no evidence for any direct DNA interaction.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	A.I.S.E.	BehalfOfAnOrganisation	463
Comment received				
A.I.S.E. supports the scientific position provided by TDMA / TDIC.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	I&P Europe - Imaging and Printing Association e.V.	BehalfOfAnOrganisation	464
Comment received				
Mutagenicity: Ames test conducted for the mixtures of toner preparations with TiO2 show negative result indicating that the toner preparations are not mutagenic. Mixtures of toner, printing ink and other imaging related chemical preparations with TiO2 are currently not classified as mutagenic agents according to the EU regulation 1272/2008/EC due to the presence of TiO2. Despite many years of production and use no cases or (eco)toxicology test results are known which indicate mutagenicity due to the use of TiO2 in coated films, specialty foils and other imaging and printing related articles. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf				
Dossier Submitter's Response				
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Australia	Australian Paint Manufacturers' Federation Incorporated	BehalfOfAnOrganisation	465
Comment received				
As above ECHA note – A non confidential attachment was submitted with the comment above. ECHA Proposed Classification of Ti02.pdf				
Dossier Submitter's Response				
See points 3 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Speciality Coatings (Darwen) Ltd	BehalfOfAnOrganisation	466
Comment received				
No issues seen by us				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	IMA-Europe	BehalfOfAnOrganisation	467
Comment received				
IMA-Europe supports the specific comments submitted by the Titanium Dioxide Manufacturers Association (TDMA) and the Titaniun Dioxide Inductry Consortium (TDIC).				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Motip Dupli GmbH	BehalfOfAnOrganisation	468
Comment received				
We fully support the TDIC and TDMA position which is no labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Germany	Stockmeier Urethanes GmbH & Co. KG	BehalfOfAnOrganisation	469
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	United Kingdom	Sun Chemical Europe	BehalfOfAnOrganisation	470
Comment received				
The evidence clearly indicates that titanium dioxide is not mutagenic or genotoxic.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany	CD-Color GmbHCo. KG	BehalfOfAnOrganisation	471
Comment received				
We have been using this substance for 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2, 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	WUK	BehalfOfAnOrganisation	472
Comment received				
No evidence of any such effect on our workers over last 45+ years.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		MemberState	473
Comment received				
It is agreed that evidence is inconclusive in terms of classification of TiO2. p. 135: Negative in vivo findings have to be more thoroughly discussed, considering lack of distribution of test material to target organs of the corresponding test				

p. 136ff: Negative in vitro findings should compare cell type differences with regard to uptake and toxicity in more detail. p.115, 122, 131, 133, 137: The quality of available data concerning oral genotoxicity should be critically discussed. This is particularly relevant for the study by Trouiller et al. (2009) p. 135 f: Data on dermal genotoxicity in vivo may be added. The study of Wu et al. (2010) should be discussed.
Dossier Submitter's Response
See point 3 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Lithuania	UAB "Veika"	BehalfOfAnOrganisation	474
Comment received				
We fully support the position provided by TDIC ant TDMA, wich is NO labeling/classification of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium	Cosmetics Europe	BehalfOfAnOrganisation	475
Comment received				
Genotoxicity The in vitro and in vivo studies performed following inhalation or intratracheal instillation of TiO2 support a secondary genotoxic mechanism through DNA oxidative damage due to the generation of reactive oxygen species. The mechanism of tumour formation in laboratory rats exposed to PSP such as TiO2 is a well-understood mechanism. The latter involves a cascade of events, triggered by "lung overload" from PSP, including sustained inflammation, production of reactive oxygen species, depletion of antioxidants, cell proliferation and eventually gene mutations. Reactive oxygen species within cells may damage DNA and potentially induce mutations. In the literature, there is a large body of evidence showing that all TiO2 materials, irrespective of their coating status, crystalline phase and particle size have no primary genotoxic or photo-genotoxic potential, in spite of the high rate of false positives observed in some in vitro tests. The IARC (2010) concluded that most of the in vitro genotoxicity studies with TiO2 gave negative results. A recent publication indicated that TiO2 nano form did not cause genotoxic effects when intravenously injected in gpt delta transgenic mice for four consecutive weeks (Suzuki et al., 2016). The studies showing a positive association between PSP exposure and genotoxicity are generally consistent with the mechanism that sub-toxic concentrations of PSP can cause inflammation and oxidative stress, which may lead to mutations. Oxidative stress is				

considered the underlying mechanism of the proliferation and genotoxic responses to PSP including TiO2 (Donaldson et al., 1996; Shi et al., 1998; Vallyathan et al., 1998; Knaapen et al., 2002; Donaldson and Stone, 2003). Given that the proliferative response is a secondary genotoxic mechanism, it is generally recognized that, for non-genotoxic carcinogens, a threshold exists such that at doses below the threshold, no toxicity is evident. The existence of a non-linear, dose-related effect with a threshold that triggers inflammation and overwhelms the body's antioxidant and DNA repair mechanisms is well described (Greim and Ziegler-Skylakakis 2007). Under conditions of particle exposure that do not overwhelm host defense mechanisms (e.g., anti-oxidants, DNA repair) and hence do not elicit inflammatory or proliferative responses, no genotoxic effects are observed.

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Greim H, Ziegler-Skylakakis K (2007). Risk assessment for biopersistent granular particles. Inhalation Toxicolology. 19(Suppl 1): 199–204.

Knaapen AM, Albrecht C, Becker A, Höhr D, Winzer A, Haenen GR, Borm PJA, Shins RPF (2002). DNA damage in lung epithelial cells isolated from rats exposed to quartz: role of surface reactivity and neutrophilic inflammation. Carcinogenesis 23(7): 1111–1120.

Suzuki, T; Miura, N; Hojo, R; Yanagiba, Y; Suda, M; Hasegawa, T; Miyagawa, M; Wang, RS (2016). Genotoxicity assessment of intravenously injected titanium dioxide nanoparticles in gpt delta transgenic mice. Mutation Research-Genetic Toxicology And Environmental Mutagenesis. 802: 30-37

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ECHA note – A non confidential attachment was submitted with the comment above. TiO2_CE input CLHPublic consultation 14072016.pdf

Dossier Submitter's Response
See point 3 of the attachment to the RCOM.
RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	476
Comment received				
Kein Effekt bekannt				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	REHAU AG + Co.	BehalfOfAnOrganisation	477
Comment received				
-				
Dossier Submitter's Response				
-				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	J.W. Ostendorf GmbH	BehalfOfAnOrganisation	478
Comment received				
see above				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Germany	Stockmeier Urethanes GmbH & Co. KG	BehalfOfAnOrganisation	479
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	WUK	BehalfOfAnOrganisation	480
Comment received				
No evidence of any such effect on our workers over last 45+ years.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany	CD-Color GmbHCo. KG	BehalfOfAnOrganisation	481
Comment received				
We have been using this substance for 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2, 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	FeRFA - The Resin Flooring Association	BehalfOfAnOrganisation	482
Comment received				
Please refer to VCI statement ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI Statement TiO2 English.pdf				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to VCI comment No. 218.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Dane Color UK Ltd.	BehalfOfAnOrganisation	483
Comment received				
No evidence from worker records ECHA note – A non confidential attachment was submitted with the comment above. TDMA response 2016-07-06.docx				
Dossier Submitter's Response				
See points 2, 3, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	I&P Europe - Imaging and Printing Association e.V.	BehalfOfAnOrganisation	484
Comment received				
Reproductive toxicity: Mixtures of toner, printing ink and other imaging related chemical preparations with TiO2 are currently not classified as repro-toxins according to the EU regulation 1272/2008/EC due to the presence of TiO2. Despite many years of production and use no cases or (eco)toxicology test results are known which indicate reproductive toxicity due to the use of TiO2 in coated films, specialty foils and other imaging and printing related articles. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf				
Dossier Submitter's Response				
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	485
Comment received				
Kein Effekt bekannt				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Lithuania	UAB "Veika"	BehalfOfAnOrganisation	486
Comment received				
We fully support the position provided by TDIC ant TDMA, wich is NO labeling/classification of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number

14.07.2016	Australia	Australian Paint Manufacturers' Federation Incorporated	BehalfOfAnOrganisation	487
Comment received				
As above ECHA note – A non confidential attachment was submitted with the comment above. ECHA Proposed Classification of Ti02.pdf				
Dossier Submitter's Response				
See points 3 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Speciality Coatings (Darwen) Ltd	BehalfOfAnOrganisation	488
Comment received				
No issues seen by us				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	REHAU AG + Co.	BehalfOfAnOrganisation	489
Comment received				
-				
Dossier Submitter's Response				
-				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	J.W. Ostendorf GmbH	BehalfOfAnOrganisation	490
Comment received				
see above				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Motip Dupli GmbH	BehalfOfAnOrganisation	491
Comment received				
We fully support the TDIC and TDMA position which is no labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Firwood Paints Ltd	BehalfOfAnOrganisation	492
Comment received				
We have no record of cases of reproductive toxicity that have been caused by our use of titanium dioxide or other powders handled in our production process.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Austria	GL Pharma	BehalfOfAnOrganisation	493
Comment received				
The same effects can be achieved with saw dust or carbon black				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom	Firwood Paints Ltd	BehalfOfAnOrganisation	494
Comment received				
We have no record of cases of respiratory sensitisation that have been caused by our use of titanium dioxide or other powders handled in our production process.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		Individual	495
Comment received				
The use of ventilation and efficient extraction and other measures of risk management in the handling of this matérial can be considered as dangerous in terms of dust are measures put in place and that work perfectly on our productions sites				
Dossier Submitter's Response				
See points 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	FeRFA - The Resin Flooring Association	BehalfOfAnOrganisation	496
Comment received				
Please refer to VCI statement ECHA note – A non confidential attachment was submitted with the comment above. 160704 VCI Statement TiO2 English.pdf				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to VCI comment No. 218.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Dane Color UK Ltd.	BehalfOfAnOrganisation	497
Comment received				
No evidence from worker records ECHA note – A non confidential attachment was submitted with the comment above. TDMA response 2016-07-06.docx				
Dossier Submitter's Response				
See points 2, 3, 4 and 5 of the attachment to the RCOM				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2016	Germany	Stockmeier Urethanes GmbH & Co. KG	BehalfOfAnOrganisation	498
Comment received				
We fully support the position provided by TDIC and TDMA, which is NO labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99				

RAC's response
Noted. See relevant response in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	I&P Europe - Imaging and Printing Association e.V.	BehalfOfAnOrganisation	499
Comment received				
Respiratory sensitisation: As stated in the general comments section, TiO2 in toner, printing ink and other imaging related chemical preparations is in the bound form and there is no evidence of respiratory sensitisation due to the presence of TiO2. Despite many years of production and use no cases or (eco)toxicology test results are known which indicate respiratory sensitisation due to the use of TiO2 in coated films, specialty foils and other imaging and printing related articles. ECHA note – A non confidential attachment was submitted with the comment above. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf				
Dossier Submitter's Response				
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Australia	Australian Paint Manufacturers' Federation Incorporated	BehalfOfAnOrganisation	500
Comment received				
As above ECHA note – A non confidential attachment was submitted with the comment above. ECHA Proposed Classification of Ti02.pdf				
Dossier Submitter's Response				
See points 3 and 5 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2016	United Kingdom	Speciality Coatings (Darwen) Ltd	BehalfOfAnOrganisation	501
Comment received				
No issues seen by us. General protection for dust in place for professional users. Medical records for many many years show no issues.				
Dossier Submitter's Response				
See point 3 and 4 of the attachment to the RCOM.				

RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2016	Netherlands	Chugoku Paints BV	BehalfOfAnOrganisation	502
Comment received				
The respirable dust will not be available once the titanium dioxide is incorporated in a paint. Even when sanding or blasting the particle size that is created will not be of such a nature that it should be considered as threat for the lungs.				
Dossier Submitter's Response				
See points 1 and 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	Motip Dupli GmbH	BehalfOfAnOrganisation	503
Comment received				
We fully support the TDIC and TDMA position which is no labelling of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	France	/	BehalfOfAnOrganisation	504
Comment received				
In paint TiO2 is embedded in a liquid matrix and is not available to cause inhalation toxicity (should the alleged toxicological effects be confirmed) when the CLP Regulation classifies based on inherent properties only. Please read the monograph about the titanium dioxyde on the IARC website. It's clearly mentionned in the monograph 93 page 210 "No significant exposure to primary particles of titanium dioxide is thought to occur during the use of products in which titanium dioxide is bound to other materials, such as in paints."				
Dossier Submitter's Response				
See points 1, 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	Germany	H. Schmincke & Co. GmbH & Co KG	BehalfOfAnOrganisation	505
Comment received				
Please see also our confidential attachment.				

Dossier Submitter's Response
See points 1, 2, 3, 4 and 5 of the attachment to the RCOM.
RAC's response
Noted. See relevant responses in the attachment to the RCOM

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2016	Germany	CD-Color GmbHCo. KG	BehalfOfAnOrganisation	506
Comment received				
We have been using this substance for 50 years and we are not aware of any relation between the use of TiO2 and the development of cancer by our workers. When handling TiO2 in powder form or when handling any powder our workers use appropriate safety equipment to protect them from dusty materials. When TiO2 has been incorporated in the tank and in the final product it is no more available to be inhaled.				
Dossier Submitter's Response				
See points 1, 2, 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
29.06.2016	United Kingdom	WUK	BehalfOfAnOrganisation	507
Comment received				
No evidence of any such effect on our workers over last 45+ years and our medical include tests to measure breathing capability.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Lithuania	UAB "Veika"	BehalfOfAnOrganisation	508
Comment received				
We fully support the position provided by TDIC ant TDMA, wich is NO labeling/classification of TiO2.				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM and response to TDMA/TDIC comment No. 99.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	509
Comment received				
Kein Effekt bekannt				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	Germany	REHAU AG + Co.	BehalfOfAnOrganisation	510
Comment received				
-				
Dossier Submitter's Response				
-				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	J.W. Ostendorf GmbH	BehalfOfAnOrganisation	511
Comment received				
We understand the risk of TiO2 powder as a common risk of all powder components and are using all of them out of this reason and hygienic reason in closed production processes: from supply in silo transporters-> transfer to Silos -> transfer to scale -> transfer to dissolvers -> until filling of the buckets.				
Dossier Submitter's Response				
See points 3 and 4 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	512
Comment received				
Kein Effekt bekannt				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				

Noted. See relevant response in the attachment to the RCOM

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany	Bundesverband Farbe Gestaltung Bautenschutz	BehalfOfAnOrganisation	513
Comment received				
Kein Effekt bekannt				
Dossier Submitter's Response				
See point 3 of the attachment to the RCOM.				
RAC's response				
Noted. See relevant response in the attachment to the RCOM				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Germany		Individual	514
Comment received				
It would make more sense that it be a generic stastement linked to the dust rather wanting to specifically linked the TiO2 to classification.Even liquid products on the basic of the use of TiO2 would be affected by the new classification , while approch linked the inhalation of dusts is based ona risk taken by the European authoritie to regulate the use of chemical substances				
Dossier Submitter's Response				
See points 1, 2, 3 and 4 of the attachment to the RCOM				
RAC's response				
Noted. See relevant responses in the attachment to the RCOM				

NON-CONFIDENTIAL ATTACHMENTS

1. 2016-07-15 laterlite reply to public consultation on TiO2.pdf
2. 2013-07-15_TiO2 CLH comment EuPC_public.pdf
3. 16 07 15 Cerame-Unie comments to the proposed classification of TiO2.docx
4. su_133_StN_WKÖ Titanoxid.pdf
5. CLH Report Comments_(confidential) 7 15 16.pdf
6. FINAL IPPIC Comments on ECHA TiO2 Consultation 7-15-16.pdf
7. JTI comments on the ANSES proposal for CLP classification of Titanium dioxide as Carcinogenic 1B (H350i).pdf
8. TiO2 - GAE comments to ECHA consultation.pdf
9. 2016-07-15 Public Consultation particip. (confidential) comm.pdf
10. Consequence of a TiO2 Ban.docx
11. Police's opinion - Polish version.pdf
12. TiO2 Stellungnahme BAH 2016_07_15.docx
13. ASCER statement on the proposal for a harmonized classification of Titanium dioxide.docx
14. 14072016_AIMPR inpult CLH Titanium dioxide-final .pdf
15. 14072016_ANFFECC inpult CLH Titanium dioxide-final .pdf
16. 14072016_FC inpult CLH Titanium dioxide-final .pdf
17. TIO2 proposal_CIAresponse FINAL.pdf

18. 14072016_EEIG. IP inpult CLH Titanium dioxide-final .pdf
19. TiO2_CLH_20160715_JCIA_EN Final.pdf
20. ANSES Proposed Classification of TiO2 - Comments by CB4REACH - 14 July 2016 - FINAL.pdf
21. Statement-HuberItalia-TitaniumDioxide.pdf
22. ECHA Proposed Classification of TiO2.pdf
23. SPI Comments on Proposed CLH for TiO2 Under the CLP Regulation.pdf
24. TiO2 - ECHA - ANAFAPYT_july_2016.pdf
25. ECHA_ CLP_Comment.pdf
26. TIP comments HCL proposal Titanium dioxide - 14072016.pdf
27. TiO2_CE input CLHPublic consultation 14072016.pdf
28. TDMA-TDIC CLH commentary_Public attachment.pdf
29. Titanium Dioxide Response to Public Consultation WSL.pdf
30. NVS final.pdf
31. FEPA_Answer to the public consultation TiO2 - July 2016.pdf
32. Clariant_Opinion on Classification Proposal for TiO2_14072016.pdf
33. CIRFS response to ECHA Consultation on Titanium Dioxide.pdf
34. MPPE Position Paper - Classification of TiO2.pdf
35. doc20160712121001.pdf
36. TiO2 - Contribution CLH Consultation - Final 12 July 2016.pdf
37. Comment to RAC of the ECHA Jochen Winkler.docx
38. ECHA Proposed Classification of Ti02.pdf
39. Statement_TiO2.pdf
40. hgD Statement_ECHA_Consultation_TiO2.pdf
41. BCF TIO2 Consultation Response.docx
42. ECETOC Cover Letter and Letter of Opinion.doc
43. Titanium Dioxide RustOleum Mathys.zip
44. Titanium Dioxide Tor Watco.zip
45. ANSES_Proposal_ IACM_Comments_July2016.pdf
46. ECHA letter.pdf
47. Titanium dioxide comments July 16.docx
48. Comments on CLH proposal from A Lansdown.pdf
49. Eurocolour input CLH Titanium dioxide_20160712.pdf
50. VdMi input CLH Titanium dioxide_20160712.pdf
51. Letter DF Titanium Dioxide 11 07 2016.pdf
52. 160704 VCI.7z
53. 160704 VCI Statement TiO2 English.pdf
54. TDMA response 2016-07-06.docx
55. Indsigelse mod klassificering af Titandioxid som kræftfremkaldende.pdf
56. Final_TEGEWA_TiO2.pdf
57. VdL-Position TiO2_30.6.2016.pdf
58. 020616_Commentary on CLH report for TiO2_DJK v2.doc
59. Comments from Colorcon to ECHA 24-June-16.pdf

CONFIDENTIAL ATTACHMENTS

1. 2013-07-15_TiO2 CLH comment EuPC_confidential.pdf
2. Brief TIO2.pdf
3. TDMA-TDIC CLH commentary_Confidential attachment.pdf
4. DECLARATION_(confidential)_2016 TiO2.pdf
5. Kestrel Building Products - Classification Proposal for Titanium Dioxide.docx
6. Swish Building Products Oppose the French Classification Proposal for Titanium Dioxide.docx
7. Contribution to the public consultation on the CLH-TiO2 report by ANSES.DOCX
8. General comments with Turnover data.pdf

9. HTAS comments on TiO CLP dossier.docx
10. Sumykhimprom - Comments on harmonized CLP of TiOx.pdf
11. Consultation TiO2_ECHA_20160706.pdf
12. ECHA Public Consultation.pdf
13. Gutachten.zip