ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 July 2019

Substance name: potassium titanium oxide ($K_2Ti_6O_{13}$)
EC number: 432-240-0
CAS number: 12056-51-8
Date of latest submission(s) considered: 29 March 2018
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressee(s): Registrant(s)[1] of potassium titanium oxide ($K_2Ti_6O_{13}$) (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), ECHA requests you to submit the following information:

1. Characterisation of the fibre content and potential to generate fibres of your registered compositions[2]:
   - Determination of presence and size distribution of fibres according to the WHO guideline (WHO, 1985), and
   - Dustiness test EN15051-2 using a rotating drum (CEN, 2016) with an analysis of presence and size distribution of fibres according to the WHO guideline (WHO, 1985).

2. If your registered composition contains ≥ 0.1% WHO fibres or can generate ≥ 0.1% WHO fibres as determined under Request 1:
   Subchronic Inhalation Toxicity: 90-day study (OECD test guideline (TG) 413, latest adopted version updated in 2018) with fibres[3] of potassium titanium oxide ($K_2Ti_6O_{13}$) in rats via the inhalation route performed according to option B of the OECD TG 413 and with:

   i) lung-associated lymph node (LALN) burden measured,
   ii) pro-inflammatory cytokines/chemokines additionally measured in the bronchoalveolar lavage (BAL),
   iii) determination of the presence of fibres in the pleura, in pleural lavage and, if relevant in fibrotic pleura wall thickening, collagen content measured in lungs and associated lymph nodes,

[1] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.
[2] Registered compositions in this decision refers to different registered compositions including different reported shape and dimensions.
[3] A fibre is defined in this decision as a particle with an aspect ratio (the ratio of length to diameter) greater than 3:1. WHO fibres are defined as fibres with fibre length (FL) > 5 µm, fibre diameter (FD) < 3 µm and aspect ratio (FL/FD) > 3 (WHO, 2000).

iv) cellular proliferation measured in lung tissue,
v) Ti-laden and fibre–laden alveolar macrophages, free fibres as well as indications of incomplete phagocytosis must be examined and recorded, if feasible.

A recovery group must be included in the design of the study with animals sacrificed one month after the end of exposure and subjected to the examinations described above.

The study protocol must be integrated with OECD TG 489 (In Vivo Mammalian Alkaline Comet Assay) in accordance with paragraph 7 of OECD TG 489, with evaluation of lung and with specific modification to detect oxidative damage.

Required test materials and specific conditions are described in detail in Appendix I.

3. If your registered composition contains ≥ 0.1% WHO fibres or can generate ≥ 0.1% WHO fibres as determined under Request 1 and if a CSR is required according to your tonnage band:
Update of the Chemical Safety Report to include the characterisation of the risks related to potassium titanium oxide fibres:

   i) Exposure assessment on fibres of potassium titanium oxide must be performed and must cover all stages of manufacture, formulation and use, for workers as well as general population, and include the emissions from brake pads, where such uses are covered by the registration dossier. Specifically, if your registration covers uses of potassium titanium oxide fibres in brake pads of cars, you are required to consider relevant reasonable worst case scenarios for the general population exposed to emissions of potassium titanium oxide fibres from automobile traffic. If your registeration covers uses of potassium titanium oxide fibres in brake pads system others than cars, e.g. train, industrial machineries, other transport system, you are required to consider relevant reasonable worst case scenarios for exposed workers (e.g. train drivers in underground confined spaces, workers in the vicinity of industrial machineries) and general population.

   ii) Derivation of a fibre-specific DNEL and fibre-specific RCR.

Deadline to submit the requested information

You must provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by the deadline indicated below.

In addition to the robust study summaries, you must submit in the update of the registration dossier(s) the full study report for the requested tests by the same deadline, by attaching them to the relevant endpoint study record in IUCLID.

The information required must be generated and provided by 24 July 2020 for request 1 and 24 October 2022 for requests 2 and 3.

Appendices

The reasons of this decision and any further test specifications of the requirements are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. Appendix 4 is confidential and not included in the public version of this decision.

Who performs the testing?

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the studies on behalf of all relevant registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

Authorised[4] by Christel Schilliger-Musset, Director of Hazard Assessment

[4] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on potassium titanium oxide ($K_2Ti_6O_{13}$) and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State competent authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health and the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested to clarify the concern for human health and environment in the follow up process.

Human health – concern related to potassium titanium oxide fibre toxicity and carcinogenicity

A "fibre" is defined in this decision as a particle with an aspect ratio (the ratio of length to diameter) greater than 3:1.

"WHO fibres" are defined as fibres with fibre length (FL) > 5 µm, fibre diameter (FD) < 3 µm and aspect ratio (FL/FD) > 3 (WHO, 2000).

<u>The concern(s) identified</u>

The identification of a potential risk is based on a combination of exposure and hazard information.

According to information in registration dossier, the Substance is used as a wear-resistant material in brake disc-pads and brake linings for cars, trains and industrial machines. Significant exposure to workers and general population cannot be excluded.

Based on information in the registration dossier and information from the published literature as detailed below, there is a concern that the Substance has carcinogenic properties.

Based on this exposure and hazard information, there is a potential risk for workers and general population. As the available information is not sufficient to conclude on potential carcinogenic properties, further information is needed, as explained below.

Indeed, potassium titanium oxide has an harmonised classification Carc. 2 under the Regulation (EC) No 1272/2008 (CLP)[5]. This classification was introduced in the context of its evaluation under the previous directive[6] (also called NONS). Carc 2 was considered

[5] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

[6] Dangerous substances Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

appropriate because of the fibrous nature of the substance and the possibility that it could split longitudinally to form long thin fibres of concern. The classification entry however applies to potassium titanium oxide without distinction of its shape, dimensions or dustiness potential.

Experimental evidence reports that a variety of fibres of different physical and chemical characteristics can elicit fibrogenic and carcinogenic effects in laboratory animals under certain exposure conditions (Vu & Lai, 1997). Important determinants of fibre toxicity and carcinogenicity are fibre dimension as well as fibre biopersistence. Fibres that are too long to be completely phagocytized by macrophages are cleared less efficiently. If fibres are not rapidly leached or broken down in the lungs, long fibres have the potential to interact with other target cells in the lungs or be translocated to the interstitium or the pleura where they may cause disease. In chronic rodent inhalation studies, fibres that persisted in the lungs caused sustained inflammation and fibrosis. These pathologic endpoints were associated in most cases with the development of lung cancer or mesotheliomas in rodents after 1–2 years (ILSI, 2005). Asbestos is classified under CLP as Carc 1A and can cause pleural diseases including mesotheliomas as well as pulmonary fibrosis and lung cancers. Refractory Ceramic Fibres (RCF) are classified as Carc 1B. Other Man-Made Vitreous Fibres (MMVF) are classified by default as Carc 2 with a possible exemption if the fibre is not biopersistent or does not show evidence of carcinogenicity in an appropriate intra-peritoneal or long-term inhalation test (note Q of the CLP entry). In particular, MMVF cannot be exempted from classification if a short term biopersistence test by intratracheal instillation has shown that the fibres longer than 20 µm have a weighted half-life longer than 40 days.

Biopersistence of potassium titanium oxide has been tested in rats over a period of 6 months after a single intratracheal (IT) instillation of 2 mg/animal of potassium titanium oxide, as reported in registration dossiers. The biological half-life in the lung was estimated to be 2.2 months, thus potassium titanium oxide can be considered as biopersistent. In another study from registration data (Adachi *et al.*, 1991), Syrian hamsters were exposed to 2 mg/animal for 5 weeks by intratracheal instillation and fibres were identified in mesenteric lymph nodes after 2 years. The biopersistence of potassium titanium oxide fibres therefore supports the concern related to their carcinogenic potential.

Potassium titanium oxide is produced and imported in EU under various compositions. Compositions in this decision refer to different compositions that include differences in reported shapes and dimensions. Some compositions contain fibres, while other compositions are not considered by Registrants to contain fibres (content in fibres below 1% w/w). However, some compositions that contain only particulates not corresponding to the definition of a fibre have been shown to generate respirable fibres when aerosolised in an experimental setting. However, information on the content or the ability to generate respirable fibres is not available for all registered compositions.

Due to the importance of the shape and dimensions of the substance on its toxicity and carcinogenicity, it is considered that hazard and risks posed by potassium titanium oxide

that contains or may generate fibres cannot be adequately characterised if hazards and risks posed by fibres of potassium titanium oxide are not appropriately characterised.

Fibres that are expected to raise the highest concern regarding their carcinogenicity are fibres fulfilling the WHO definition (fibre length (FL) > 5 µm, fibre diameter (FD) < 3 µm and aspect ratio (FL/FD) > 3), although it is not fully excluded that fibres that do not fulfil WHO definition may also present some carcinogenic hazard.

A 90-day study of adequate reliability is available on potassium titanium oxide in the registration data. The bulk test material used in this study did not contain WHO fibres (mean D: 41 µm; mean L: 113 µm). However, monitoring of the atmosphere in the exposure chambers measured a proportion of 6.4 to 7.4% of WHO fibres. Test particules in exposure chambers had a mean diameter of 0.65 to 0.94 µm and a mean length of 2.00 to 2.94 µm. Rats were exposed to concentrations of 5, 50 or 500 mg/m^3 of bulk material. Observed histological effects consist mainly in thickening of alveolar wall from 50 mg/m^3. This study indicates that the WHO fibres can be generated from some compositions of potassium titanium that do not initially contain the WHO fibres, when manipulated. Nevertheless, toxicity and carcinogenic potential of potassium titanium oxide fibres can only be appropriately characterised if animals are exposed to a sufficient dose of fibres (ILSI, 2005). The WHO fibre content in this study is considered insufficient to appropriately achieve that aim.

There is no carcinogenicity study available on potassium titanium oxide.

Registration data also report studies from literature performed on the closely related potassium octatitanate ($K_2Ti_8O_{17}$) and provides information on its carcinogenic potential:

- In a two-year inhalation study in Fischer 344 rats, no significant increase in lung tumours or mesotheliomas was reported in the registration data (Ikegami *et al.*, 2004). The highest dose was however low (0.545 mg/m^3, 200 WHO fibre/cm^3). Whereas non-neoplastic changes were observed in the lung, no significant effect on body weight, mortality and no clinical signs were reported. The absence of effects may be related to the low dose tested and this study is therefore considered by the evaluating MSCA as inappropriate to definitely conclude.
- After intrapleural implantation of a single dose (40 mg/rat), 2 fibrous potassium octatitanates induced tumours in 21/29 and 20/29 Osborne-Mendel rats after 2 years. According to registration data, the incidence was similar to crocidolite and silicon carbide and proportionate to the number of fibres with a length>8 µm and a diameter<0.25 µm (Stanton *et al.*, 1981). By a similar route, a recent study (Yokohira *et al.*, 2016) did not report tumours in 11 Fischer 344 rats (30 mg/rat) but with a shorter observation period of 1 year. In this study, different strains of mice were tested (3 mg/mouse). 2/22 ICR mice had lung tumours. No tumours were observed with 3 other strains (A/J, C3H and C57BL; 12, 7 and 9 animals tested, respectively). The interpretation of this latter result is however limited by a follow-up period of only 415 days in mice. The differences obtained in these two intrapleural studies are

however not fully explained.

- After a single intraperitoneal injection of 5 or 10 mg/animal and 2-year observation, mesothelioma incidence was 20 and 77% of treated Fischer 344 rats, respectively. According to registration data, the incidence was intermediate between RCF and silicon carbide and chrysotile (Adachi *et al.*, 2001).

The difference in response in the different studies may in some cases be attributed to differences in the shape and size of the test material. Experimental conditions vary across studies and may impact study outcomes. Comparison of subchronic data performed with either potassium octatitanate or potassium hexatitanate indicates that potassium hexatitanate may be less prone to induce histological effects in the lung and octatitanate can be considered as a relevant worse case for hexatitanate. Nevertheless, the variability in results for octatitanate is not fully understood.

Altogether, data from potassium octatitanate therefore also support that carcinogenicity of potassium titanium oxide fibres (hexatitanate) is a concern and should be clarified. But based on the existing database, the suspected carcinogenic potential of potassium titanium oxide fibres cannot be properly addressed.

Potassium titanium oxide is produced and imported in the European Union (EU) by several registrants up to the tonnage band of 100-1000 Tpa. It is used in the formulation of articles, mainly as reinforcement in the friction material of automobile brake pads. Therefore, there is an exposure potential for workers during manufacture and use. Possible exposure of the general population is further discussed below.

The carcinogenic hazard and risk related to potassium titanium oxide fibres need to be clarified for the sake of worker health protection and possibly general population protection.

This decision aims to further characterise the carcinogenicity concern of the registered potassium titanium oxide compositions that may lead to an exposure to potassium titanium oxide fibres, that is to say registered compositions containing more than 0.1% w/w fibres fulfilling the WHO criteria or which may release more than 0.1% w/w fibres fulfilling the WHO criteria during their life cycle.

1. **Characterisation of the fibre content and potential to generate fibres of your registered compositions[7]:**
   - **Determination of presence and size distribution of fibres according to the WHO guideline (WHO, 1985), and**
   - **Dustiness test EN15051-2 using a rotating drum (CEN, 2016) with an analysis of presence and size distribution of fibres according to the WHO guideline (WHO, 1985).**

Test material

Each composition of each Registrant must be characterised.

Why new information is needed

The carcinogenic concern relates specifically to fibres and the requests 2 and 3 are relevant if there is an exposure potential to fibres through presence of fibres in registered compositions or possible formation of fibres during handling and use. Therefore, characterisation of fibre content and potential to generate fibres is a prerequisite to the clarification of the concern.

What is the possible regulatory outcome

This characterisation step will define whether the WHO fibres are present in or can be generated from the registered compositions and thus whether the requests 2 and 3 related to fibre toxicity apply.

Requests 2 and 3 further discussed below are requested if the WHO fibre content of your registered compositions is equal or above 0.1% WHO fibres or if they can generate a WHO fibre content equal or above 0.1%. The threshold for the requests is 0.1% because the concern relates to clarification of the potential of fibres to be presumed carcinogen (category 1B). For the classification of a mixture as a carcinogenic, category 1 under the CLP Regulation, the general concentration limit of an ingredient triggering that classification is at or above 0.1% and the concern therefore exists when fibres are present ≥ 0.1%.

Consideration on the test method and testing strategy

The analysis of size distribution must be performed in accordance with the WHO guideline "Reference methods for measuring airborne man-made mineral fibres (MMMF)" (WHO, 1985). Electron microscopy must be used to determine size distribution. Larger diameters can be measured by using lower SEM magnifications but the method will be increasingly limited for finer fibre distributions and a TEM (transmission electron microscope) measurement is recommended if the median diameter is below 0.5 µm.

[7] Registered compositions in this decision refers to different registered compositions including different reported shape and dimensions.

The total fibre content and WHO fibre content must be determined for each composition.

Consideration of alternative approaches

No alternative approach is considered relevant to address the concern.

Consideration of your comments on the original draft decision, of PfAs and of your comments to the PfAs

A PfA proposed that information initially listed as an exemption criteria (characterisation of fibre content) is requested as a first step of the test strategy instead. You expressed a preference for removal of the exemptions so that all Registrants are involved in the study. You also recognised the need to test for fibrosity of the substance from 0.1%. The requests 2 and 3 are related to fibre toxicity and may not be legally justified for all Registrants. Therefore, it is necessary to characterise the fibre content and potential to generate fibres of the different registered compositions and to define conditions that further trigger requests 2 and 3 to clarify the concern related to fibres. The structure of the decision has therefore been changed to require characterisation of fibre content as a initial step.

Conclusion

Therefore, you are requested to characterise the fibre content and potential to generate fibres of your registered compositions, as specified above**.**

2. **Subchronic Inhalation 90-day Toxicity (OECD 413) with an integrated Comet assay (OECD 489)**

Test material

The aim of the request is to appropriately characterise the toxicity and carcinogenic potential of potassium titanium oxide fibres and this can only be achieved if animals are exposed to a sufficient dose of fibres.

Indeed, due to the importance of the shape and dimensions of the substance on its toxicity and carcinogenicity, it is considered that hazard and risks posed by potassium titanium oxide that contains or may generate fibres cannot be adequately characterised if hazards and risks posed by fibres of potassium titanium oxide are not appropriately characterised.

Fibres that are expected to raise the highest concern regarding their carcinogenicity are fibres fulfilling the WHO definition (fibre length (FL) > 5 µm, fibre diameter (FD) < 3 µm and aspect ratio (FL/FD) > 3), although it is not fully excluded that fibres that do not fulfil WHO definition may also present some carcinogenic hazard.

Testing of the registered composition of the substance is not expected to allow clarifying the concern specifically associated to fibres as the registered composition of potassium

titanium oxide may not contain a sufficient amount of the WHO fibres to provide clear characterisation of fibre toxicity.

Therefore, the test material for this request is fibres of potassium titanium oxide with specific objectives in terms of the number of fibres of certain size, as discussed below.

ECHA, together with the evaluating Member State, offers you the opportunity for an informal discussion after completion of request 1 to provide contextual clarification that may be useful for determining the appropriate test material for the execution of request 2.

Although it might not correspond to a registered composition as such, testing of potassium titanium oxide fibres and WHO fibres in particular is considered technically feasible as WHO fibres are contained in potassium titanium oxide or may be generated from the registered compositions. In addition, historically, potassium titanium oxide was exclusively produced as fibres. Results from the requested study are not expected to be used directly to characterise the toxicity and carcinogenic potential of the substance placed on the market as a whole but are necessary for the adequate determination of hazard and risks of potassium titanium oxide on the market that contains or may generate the WHO fibres. This approach is consistent with the request 3 of the decision that aims to develop a characterisation of risk related specifically to the hazard of and exposure to the fibre fraction present in the substance on the market or generated during use.

Why new information is needed

As discussed above in the section "The concern(s) identified", potassium titanium oxide may contain or generate respirable fibres. Potassium titanium oxide fibres are biopersistent and may exert carcinogenic effects stronger than corresponding to the existing harmonised classification. This is further supported by positive results from the closely related potassium octatitanate. However, based on the available database, no definite conclusion can be drawn for potassium titanium oxide fibres. Registrant(s) have expressed the request that the harmonised classification Carc 2 of potassium titanium oxide is reconsidered. In the perspective to refine the classification of potassium titanium oxide depending on its shape and dimension, a prerequisite is to better characterise the carcinogenicity of potassium titanium oxide containing or forming fibres fulfilling WHO criteria.

In addition, due to the importance of the shape and dimensions of the substance on its toxicity and carcinogenicity, it is considered that hazard and risks posed by potassium titanium oxide that contains or may generate fibres cannot be adequately characterised if hazards and risks posed by fibres of potassium titanium oxide are not appropriately characterised. Because of the potential exposure of workers, carcinogenic properties of potassium titanium oxide fibres need to be clarified by appropriate studies and a 90-day study with an appropriate design is considered as an essential preliminary step.

What is the possible regulatory outcome

Potassium titanium oxide is currently classified under CLP as a suspected human carcinogen (Carc 2) on the basis of formation of respirable fibres. Due to their biopersistence, potassium titanium fibres may exert carcinogenic effects that warrant a more stringent classification Carc 1B. Nevertheless, this needs to be supported by relevant experimental data but, no carcinogenicity study is yet available to discard or confirm and better characterise the carcinogenic properties of potassium titanium oxide containing or forming fibres fulfilling the WHO criteria.

A classification as Carc 1B has different downstream consequences compared to a classification Carc 2. In particular under the Occupational Safety and Health (OSH) legislation, provisions of the Carcinogens and Mutagens Directive 2004/37/EC apply to Carc 1B substances and provides reinforced prevention rules to protect workers health, in particular through substitution, reduction of exposure to a minimum, health surveillance of workers and binding occupational exposure levels.

Considering that not all compositions of potassium titanium oxide contain or possibly generate fibres, a clear identification of its carcinogenic potential of fibres would also encourage the substitution toward these compositions. As mentioned above and depending on the compositions, the existing classification can possibly be both over- and/or underprotective and a revision of the classification could be considered.

The requested 90-day repeated dose toxicity study with an integrated Comet assay is an indispensable prerequisite to define whether a carcinogenicity study would need to be requested by the way of a new decision. That new decision would be warranted if there is still a need to clarify the carcinogenicity concern with a view of appropriate classification for that hazard. For further details, see section below.

Additionally, a restriction of uses could be envisaged if a risk is demonstrated, in particular in relation to general population.

Finally, the requested new information will allow to better characterise the risk related to potassium titanium oxide containing or forming fibres fulfilling the WHO criteria by considering specifically the toxic and carcinogenic properties of its fibres, and to define adequate risk management measures if necessary.

Considerations on the test method and testing strategy

Subchronic Inhalation 90-day Toxicity (OECD 413)

The study must be performed by inhalation route as it is the most relevant route for human exposure to fibres. Administration must be performed by nose-only exposure to avoid oral uptake of the substance. The test must be performed in rat, which is the preferred test species due to the large historical database. The rat strain used must be consistent with

JRC recommendations (JRC, 1999).

A subchronic toxicity assay (90-day study) is required for investigating further the carcinogenicity potential of the registered substance. Although it can not fully characterise the carcinogenic potential of potassium titanium oxide fibres, it may provide important information on the pathogenic and carcinogenic potential of fibres in the respiratory tract.

If results of the subchronic study provides evidence that potassium titanium oxide fibres can induce effects considered to be involved in the development of a carcinogenic response with longer exposure to biopersistent fibres, a subchronic toxicity study might not be sufficient to fully characterise the carcinogenic potential of potassium titanium oxide fibres. A carcinogenic study might be necessary to decide if the substance meets the classification criteria as Carc 1B. Further to the evaluation of the outcomes of the 90-day study by the evaluating MSCA, a full carcinogenicity study may therefore be required in the next phase of the substance evaluation.

The OECD TG 413 study must be performed according to option B of the guideline that is recommended when test substance are likely to be retained in the lung.
The following parameters, that are relevant to understand fibre pathogenic potential, must be collected during the OECD TG 413 study:

- Lung-associated lymph node (LALN) burden must be determined to inform on alternative clearance routes, in accordance with OECD TG 413 that mentions that deposition of particles in LALN must always be determined as indicator of translocation when testing poorly soluble particles.

- Bronchoalveolar lavage (BAL): inflammation is a common feature of fibre toxicity that may be involved in the development of lesions such as fibrosis and tumours. Inflammation can be evaluated quantitatively using BAL parameters (US EPA, 1995; IARC, 2002; ILSI, 2005; WHO, 2008). In addition to parameters recommended in option B of the TG 413 (total and differential leukocyte counts, total protein, lactate dehydrogenase), pro-inflammatory cytokines/chemokines must be measured to appropriately monitor the inflammatory response.

- Pleural lavage: a high incidence of pleural mesothelioma were observed with potassium octatitanate after intrapleural or intraperitoneal administered according registration data (Stanton *et al.*, 1981; Adachi *et al.*, 2001) and the possible translocation of fibres into the pleura and toxicological responses in the pleural region must de determined. The presence of fibres in the pleura, in pleural lavage and if relevant in fibrotic pleura wall thickening must be examined. Procedures of pleural lavage are described in Oberdörster *et al.* (1983) and in Gelzleichter *et al.* (1996).

- Collagen content (fibrosis). Although the role of fibre-induced fibrosis in carcinogenicity is not clear, fibrosis is an adverse effect that is relevant to assess hazard of fibres to

human health in short-term experiment (ILSI, 2005; WHO, 2008). Measure of collagen content provides further information on possible repair mechanisms in place.

- Cellular proliferation. Proliferation of target cells for carcinogenicity above background levels can be regarded as an essential step in carcinogenesis (WHO, 2008) and is a relevant endpoint to include in subchronic animal experiments with fibres. Cell proliferation in the lung can be measured using antibodies against Proliferating Cell Nuclear Antigen (PCNA) (Abdelgied *et al.,* 2019).

As an additional requirement, Ti-laden and fibre–laden alveolar macrophages, free fibres as well as indications of incomplete phagocytosis must be examined and recorded, if feasible.

A recovery group must be included in the design of the study with animals sacrificed 1 month after the end of exposure and subjected to examinations described above.

You must ensure that exposure concentrations are adequate, i.e. that animals are exposed to a sufficient number of fibres of adequate dimension. However, to avoid effects due to overload of non fibrous material, excessively high gravimetric doses must be avoided. Therefore, it is necessary to determine doses both as w/w percentage in the atmosphere as well as the fibre number. Size distribution and number of WHO fibres must also be determined. Determination of fibre amount and distribution in the test substance may require electron microscopy techniques to overcome the limited resolution of phase-contrast microscopy for detection of (translucent) thin fibres. Adequate level of exposure, in terms of number of fibre and maximum gravimetric concentrations are defined in the EC guideline for subchronic inhalation toxicity testing of fibres (JRC, 1999):

- 15 fibres/cm^3 longer than 20 µm in length with a GMD as close as possible to 0.8 µm
- 50 fibres/cm^3 longer than 20 µm in length with a GMD as close as possible to 0.8 µm
- 150 fibres/cm^3 longer than 20 µm in length with a GMD as close as possible to 0.8 µm
- the gravimetric mean concentration of those fibres should not exceed 40 mg/m^3, if technically feasible
- the gravimetric concentration of all particles (fibrous and non-fibrous) in the test atmosphere should not exceed 60 mg/m^3, if technically feasible.

It also provides recommendation to adapt the number of fibre depending on the density of the material.

These recommendations must be applied as far as technically possible. In any case, the test material must contain a sufficient number of fibres with the highest range of lengths that can be generated.

Integrated in Vivo Mammalian Alkaline Comet Assay (OECD 489) on lung tissue, with specific modification to detect oxidative damage.

Genotoxicity has been proposed as a possible contributing mechanism to fibre carcinogenic effects. In particular, genotoxicity may result from fibre-derived free radicals that can form DNA adducts such as 8-hydroxy-deoxyguanosine (8-OH-DG). It may also result indirectly from chronic inflammatory reactions leading to the prolonged release of Reactive Oxygen Species (ROS) that can produce adducts, single- and double-strand breaks and DNA crosslinks (ILSI, 2005). The Comet assay has shown its ability to capture genotoxic response of asbestos fibres (Jung et al., 2000) and long needle-like multi-walled carbon nanotubes (FIOH, 2013). Inclusion of a Comet assay in lung tissue is therefore intended to provide relevant information on possible pathological events in the 90-day study and must be integrated to the study as far as technically possible.

In addition to the standard protocol as described in OECD test guideline 489, the sensitivity and specificity of the assay to oxidative damage can be improved by incubating the lysed cells (nucleoids) with lesion-specific endonucleases, which recognize different types of oxidative damage (Collins, 2014). The test thus must be complemented to identify oxidative DNA damage by using an exogenous DNA repair enzyme such as human 8-hydroxyguanine DNA-glycosylase (hOGG1) or the formamidopyrimidine DNA-glycosylase (FPG). These enzymes recognise and remove oxidatively damaged purines, for example, 8-oxo-7,8-dihydroguanine formamidopyrimidine moieties. In particular, hOGG1 has been proven to be specific to 8-OH-DG (Smith et al., 2006). It is therefore requested to perform the Comet assay with and without addition of a specific endonuclease (hOGG1 or FPG) to improve detection of oxidative damage. The modification of the protocol consists to add additional slides in the standard alkaline comet assay (OECD TG 489) which will be treated with enzyme (hOGG1 or FPG) between the lysis and alkaline treatment. It is recommended to use the protocol based on the publications from Ersson *et al.* (2013) and Dusinska (2000). In addition, further technical specification to help you to do the method succesfully is suggested:

- Dilution of the enzyme in dilution buffer (IU/mL), amount of the diluted enzyme applied to comet preparations, and incubation time of comet assay slides with enzyme at 37 °C should be carefully determined to guarantee maximum dynamic range between negative and positive control slides. Positive controls should be obtained by treating the comet assay slides prepared by agarose embedding of the tissues isolated from negative control animals prior to lysis such as RO 19-8022 treatment followed by light induction (Collins, 2014).
- With regards to the number of slides, it is recommended to prepare 2 sets of slides for each test condition: one set submitted to the standard protocol (without enzyme), the other submitted to a modified protocol (with enzymes). The enzyme buffer (without enzyme) will serve as control.

Any deviations from this suggested protocol should be scientifically justified. It is also noted for consideration that techniques to improve the Comet assay in the lung has been published recently (Jackson *et al.*, 2013).

The Comet assay is requested to be conducted at the end of the 90-day exposure period but not in the recovery group.

It is the responsibility of the Registrants to ensure that a combination of the 90-day study and of the Comet assay does not impair the validity and the results of the information of each study. In particular, specific attention should be given to sampling times for the different analysis.

In this aim, the following design that consider issues related to adequate sampling times for the different analyses is suggested, although it remains the responsibility of the Registrants to define the final design depending on practical feasibility:

- Histopathology (including LALN parameters, determination of collagen content, cell proliferation and pleural investigations) and Comet assay can be performed in the main study, with sacrifice of the animals at a sampling time appropriate for the Comet assay (6-12 hr after the end of the 90-day exposure).
- Lung burden and assessment of BAL can be determined in a satellite group (animals sacrificed 24 hr after the end of the 90-day exposure).
- BAL, lung burden and histopathology (including LALN parameters, determination of collagen content, cell proliferation and pleural investigations) must be performed in animals of the recovery group, as recommended in option B of OECD TG 413 at post-exposure observation 2 (PEO-2).

Consideration of alternative approaches

The request for this study is suitable and necessary as a prerequisite to obtain information that will allow to clarify carcinogenic risk in a potential future request under substance evaluation. More explicitly, there is no equally suitable alternative way available of obtaining this information. In particular, ECHA notes that there is no alternative experimental protocol available at this stage that will generate the necessary information without using vertebrate animals.

Consideration of your comments on the original draft decision, of PfAs and of your comments to the PfAs

You commented on the tiered testing strategy for clarification of the carcinogenic properties of the substance and on the deadlines for testing (fibres content, 90-day study). The strategy of the requests was therefore adapted by removing the initially requested carcinogenicity testing from the present decision, clarifications on the testing strategy were added and deadlines for providing the information were refined to accommodate your concerns. The evaluating MSCA will assess whether the results of the 90-day study with an integrated comet assay and with the requested additional parameters trigger a need for a carcinogenicity study in a subsequent decision.

Regarding your comments relating to consequences for the market of the products containing the Substance, you can refer to ECHA's "Guidance in a Nutshell on requirements for substances in articles" and "Guidance in a Nutshell for Downstream users". As for your comments concerning the possible cease of manufacture of the Substance, please consult "ECHA's Practical Guide on How to act in substance evaluation" in relation to Article 50(3) of REACH.

You furthermore commented that the requested test material does not reflect the hazard properties of the Substance placed on the market leading to overestimation of the carcinogenic potential of the Substance. However, the purpose of testing is to characterise the toxicity and carcinogenic potential of fibres of potassium titanium oxide. Those fibres are part of the Substance placed on the market or can be generated during life cycle (friction of brake pads). It is necessary to determine the carcinogenic potential of this fraction of the Substance and consider it in the adequate determination of hazard and risks of potassium titanium oxide, taking into account the concentration of fibre contained or generated.

A Proposal for Amendment (PfA) considered that reference to Art. 6(3) of CLP was not relevant and you supported this comment and deletion of references to complex substances. The text was modified to delete the term 'complex substance' and reference to Article 6(3) to CLP.

A PfA suggested to use the threshold of 0.1% (instead of 1%) to define the fibre content below which the requests related to fibres do not apply. You disagree with this proposal as you consider it would be a prejudice to testing outcome in relation to the carcinogenicity of fibres. However, the concern relates to clarification of the potential of fibres to be presumed carcinogen (category 1B) and the concern therefore exists when fibres are present above 0.1%.

A PfA suggested to perform a long-term (2-year) study by intraperitoneal (IP) route as an alternative to discriminate effects of fibres from effects of granular particles. You asked that this point is commented. Positive IP studies are not consistently reflected by positive chronic inhalation studies (Drummond, 2016). Different carcinogenic responses to chronic inhalation exposures of humans and rats to some asbestos fibres are observed but becomes coherent when current knowledge of the influences of fibre type, dimensional distributions and biopersistence are taken into account (Lippmann, 2014). The 90-day inhalation study is expected to provide informative data on the onset of a pathogenic response to fibres. In addition, there are uncertainties on how IP study can be used for classification purpose. Inhalation is also the preferred route of exposure to obtain data through a relevant route of exposure for humans that may also be used for risk assessment.

A PfA commented that estimation of fibre amount may require electron microscopy. You requested a clarification as phase-contrast optical microscopy (PCOM) was also mentioned and questioned relevance of EU method A.22. The EU method A.22 is not suitable as it

does not determine size distribution. The reference method is WHO guideline (WHO, 1985) that refers to electron microscopy for size determination. This technique is therefore relevant for request 1 as well as for determining size distribution in the 90-day study.

PfAs related to the design of the study were submitted. In particular, reference to the updated OECD TG 413 (June 2018), specifications of the nose-only route of exposure and of the lung as target organ for the Comet assay were suggested and supported by you. Addition of additional fibre—specific endpoints was also suggested. These changes were implemented in the Decision.

PfAs, that you supported, were submitted to clarify requirements related to definition of appropriate levels of exposure and definition of test material. It is not possible to be prescriptive in terms of fibre content or doses as it needs to be adapted considering specific properties of the test substance in the preliminary phase of the study. The objective of the study is to characterise the toxicity of the fibre fraction of the substance. To achieve that aim, it has been clarified that the recommendations published by JRC for a subchronic inhalation toxicity study of synthetic mineral fibres in rats (JRC, 1999) must be applied to define the appropriate level of doses, both in terms of fibre number and of gravimetric concentrations. The possibility to have an informal discussion with ECHA and the evaluating MSCA after completion of request 1 to provide contextual clarification that may be useful for determining the appropriate test material for request 2 has also been included.

PfAs commented on the difficulty to integrate the Comet assay to the 90-day inhalation study without compromising the reliability of both studies and you asked to better define the testing protocol details. It was clarified that the Comet assay is intended to provide information on possible pathological events in the 90-day study and should be integrated as far as possible. A refined, more detailed protocol has been proposed. However, the responsibility to define the final protocol lies with the Registrants.

A PfA, that you supported, suggested to extend the deadline to apply the updated OECD 413 guideline. The complexity to generate the test material and to define an integrated protocol is recognised and the time allocated for this study was extended from 18 to 24 months.

Conclusion

Therefore, you are required to carry out the following study using fibres of the substance subject to this decision:

> If your registered composition contains ≥ 0.1% WHO fibres or can generate ≥ 0.1% WHO fibres as determined under Request 1:
> Subchronic Inhalation Toxicity: 90-day study (OECD test guideline (TG) 413, latest adopted version updated in 2018) with fibres of potassium titanium oxide ($K_2Ti_6O_{13}$) in rats via the inhalation route performed according to option B and with:

i) measurement of lung-associated lymph node (LALN) burden,
ii) pro-inflammatory cytokines/chemokines additionally measured in the bronchoalveolar lavage (BAL),
iii) determination of the presence of fibres in the pleura, in pleural lavage and, if relevant in fibrotic pleura wall thickening, collagen content measured in lungs and associated lymph nodes,
iv) cellular proliferation measured in lung tissue,
v) Ti-laden and fibre–laden alveolar macrophages, free fibres as well as indications of incomplete phagocytosis must be examined and recorded, if feasible.

A recovery group shall be included in the design of the study with animals sacrificed one month after the end of exposure and subjected to the examinations described above. The study protocol shall be integrated with OECD TG 489 (*In Vivo* Mammalian Alkaline Comet Assay) in accordance with paragraph 7 of OECD TG 489, with evaluation of lung and with specific modification to detect oxidative damage.

3. Exposure assessment and characterisation of risks related to potassium titanium oxide fibres

Why new information is needed

Potassium titanium oxide fibres may exert toxic effects that are specific to the fibre shape and dimension, in particular carcinogenic effects. Exposure and risk assessments related to potassium titanium oxide fibres is either missing or insufficient in the existing Chemical Safety Report (CSR) and should be determined at all stages of manufacture, formulation and use, for workers as well as general population, where such uses are covered by the registration dossier.

In particular, it has been shown that non-exhaust traffic related particules contribute almost equally to exhaust-related related particles and brake wear contributes to 16-55% by mass to total non-exhaust traffic related PM10 emissions in urban environments (JRC, 2014). Emission through the use of brake pads is therefore a relevant source of exposure to consider.

Garg *et al.* (2000) performed a dynamometer assay including two brake pads containing potassium titanium oxide. A low amount of fibres were measured. However, the definition of a fibre in the study was more restrictive than the definition of the WHO fibre and may have led to an underestimation. In addition, due to the variability in shape, dimension and fibre content across registered compositions of potassium titanium oxide, the representativity of this result for each registered composition is not known.

Therefore, the potential release and exposure to potassium titanium oxide fibres that may

be generated by friction of brake pads must be assessed in the CSR, especially in view of its Carc 2 classification.

What is the possible regulatory outcome

Potassium titanium oxide has already an harmonised classification Carc. 2 and characterisation of exposure for all exposed populations may trigger the need to consider restriction of the substance. In addition, an appropriate characterisation of the exposure and risks of its use in brake pads will allow to adequately adjust operational conditions or consider further risk management measures to limit exposure of the general population and/or workers.

Considerations on the test method and testing strategy

Exposure assessment on fibres of potassium titanium oxide must cover all stages of manufacture, formulation and use, for workers as well as general population, and include the emissions from brake pads, where such uses are covered by the registration dossier.

In particular:

- If your registration covers uses of potassium titanium oxide fibres in brake pads in cars, you are required to consider relevant reasonable worst case scenarios for general population exposed to the chronic release of potassium titanium oxide fibres from automobile traffic.

- If your registration covers uses of potassium titanium oxide fibres in brake pads system others than cars, e.g. train, industrial machineries, other transport system, you are required to consider relevant reasonable worst case scenarios for exposed workers (e.g. train drivers in underground confined spaces, workers in the vicinity of industrial machineries) and general population.

The assessment of exposure to potassium titanium fibres must be in line with exposure assessment and risk characterisation laid down in Article 14(4) of REACH and in ECHA's Guidance R.14 for occupational exposure and R.15 for consumer exposure. For outdoor uses, Guidance R.16 related to environmental exposure is also relevant to consider. Airborne exposure must be expressed in fibre number/cm^3.

Generation of experimental data, such as brake dynamometer assay can be considered to improve the characterisation and quantification of emission under more realistic conditions. The experimental data should cover an appropriate sequence of braking events to provide data representative of reasonable worst cases. In particular, speed, frequency and duration of brake application and temperature of brake surface should be considered. Representativeness of the brake pads tested should also be discussed. Airborne fibres should be collected and counted with an analysis of size distribution by electron microscopy in accordance to the WHO guideline (WHO, 1985). Diffraction or any appropriate analytical method should be used to confirm that collected fibres are potassium titanium oxide fibres.

The experimental measurement of very low WHO fibre emission from brake pads, may allow you to justify not to perform a quantitative exposure assessment for certain exposure situations.

Derivation of the fibre-specific DNEL must consider the results of request 2.

You are not required to provide any information under this request 3, if you are not required to produce a CSR according to your tonnage band.

Consideration of alternative approaches

No alternative approach is considered relevant to address the concern as the knowledge of the exposure conditions that best reflect the conditions of use of the substance is not available to the eMSCA.

Consideration of your comments on the original draft decision, of PfAs and of your comments to the PfAs

No comments were provided in relation to request 3.

A PfA was submitted to propose the removal of the request. The PfA considered that characterisation of exposure during the whole life cycle (brake pads) is already a part of the obligations of Registrants under REACH. The information request should not go beyond Registrants' control. You supported these considerations of the PfA, but informed that an update of the CSR based on your best knowledge is intended.

The present request is targeted at the concern related to relevant fibres and can therefore be requested in substance evaluation under Article 46 of REACH. Additional text has been inserted to ensure that the information request does not go beyond the Registrants' control and what the registrations should cover.

Conclusion

Therefore, you are required to provide an exposure assessment and risk characterisation of fibres of potassium titanium oxide, as specified above. This applies if your registered composition contains ≥ 0.1% WHO fibres or can generate ≥ 0.1% WHO fibres as determined under Request 1 and if a CSR is required according to your tonnage band.

Full study reports

Considering the complexity and specifity of the case, a complete rationale and access to all information available in the full study reports (implemented method, raw data collected, characterisation of the material tested, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed for requested studies. This will allow the evaluating MSCA to fully assess the provided information, including the statistical analysis, and to efficiently clarify the concerns.

Deadline

The time lines for provision of the requested data take into account the time that you may need to agree on which of the registrant(s) will perform the required tests (3 administrative months are allocated for this) and include the time required for developing an analytical method, the WHO-fibre characterisation, conduct of the study according to the specified test guideline OECD 413 with an integration of OECD 489, preparation of the study report and reporting in IUCLID.

The deadlines are based on the following tiered approach:

The request for the WHO-fibre content characterisation is deemed to be performed within 9 months, with an additional 3 administrative months summing up to 12 months.

Subsequently, in the second tier, the specified 90-day study with integrated comet assay testing (OECD TG 413 + 489) shall be performed, if relevant. It is considered adequate to allow 24 months for this testing. With additional 3 months administrative time, this second tier sums up to 27 months.

Overall, if all testing tiers need to be performed, the final deadline for the information to be provided is 39 months. Otherwise, if the second tier (OECD TG 413 + 489) is not applicable, the final deadline for the information to be provided is 12 months.

Thus, the deadline considers the complexity to generate the test material and to define an integrated protocol for the inhalation study. Your comments concerning prolongation of time to perform the study according to the test guideline OECD 413 with an integration of OECD 489 are accommodated.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to carcinogenicity and exposure of workers, potassium titanium oxide ($K_2Ti_6O_{13}$) CAS No 12056-51-8 (EC No 432-240-0) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2017. The updated CoRAP was published on the ECHA website on 21 March 2017. The competent authority of France (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding exposure of the general population and potassium titanium oxide toxicity on sediment-dwelling organisms.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 21 March 2018.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation as described below.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). The requests were partly amended and clarifications on the testing strategy were added and deadlines were refined.

Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.
Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified partly the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

MSC agreement seeking stage

During MSC meeting, it was agreed to remove the request on long-term toxicity to sediment organisms (OECD 225) with the registered substance as being premature. The evaluating MSCA may consider asking for further environmental tests after a new phase of evaluation.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-64 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study on behalf of the other registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

4. Further advice can be found at: http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them.