COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Substance name: divanadium pentaoxide; vanadium pentoxide
CAS number: 1314-62-1
EC number: 215-239-8
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany	Vanadium Consortium / Vanitec	Industry or trade association	1
Comment received				
The Vanadium industry, represented by Vanitec and the Vanadium Consortium, takes this opportunity to submit scientific comments on the Proposal for Harmonised Classification and Labelling of divanadium pentaoxide. Our comments are put forward in detail endpoint-by-endpoint in the public attachment" Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf". We propose an alternative science-based, justifiable classification since we disagree with the unbalanced analysis, methodology, and findings in the CLH proposal ECHA note – An attachment was submitted with the comment above. Refer to public attachment Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Spain	Frit Consortium	Industry or trade association	2
Comment received				
The Frit Consortium is the organization that manages the REACH and CLP obligations of companies that manufacture or import frits into the EU. The Consortium currently includes 34 members from different European countries, mainly Spain, Italy and Germany. The members of the Frit Consortium are the largest producers in Europe for frits. Frits are chemical substances, result of a mixture of inorganic chemical substances (typically consisting of metal oxides and salts) 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. Divanadium pentaoxide and other vanadium compounds are used as important raw materials for some specific types of frits and cannot be substituted. During the manufacturing process, raw materials are transformed via melting and the resulting substances contain vanadium ions confined into the vitreous structure of the frit. These substances are exclusively manufactured at industrial sites by trained workers and their main end uses are ceramics, glass and				

metals.

The Frit Consortium fully supports the scientific and technical position of the Vanadium REACH Consortium in relation to the current Public Consultation to modify the existing entry for divanadium pentaoxide in Annex VI of the CLP Regulation.

Impact of the CLH proposal in our sector:
The proposed harmonised classification and labelling for divanadium pentaoxide would have a negative impact in our sector mainly due to its use as raw material, but also due to potential stigmatisation of vanadium-containing frits.
The following main consequences have been identified:
- Changes in the manufacturing and handling practices
- Market impact due to stigmatisation of all substances and mixtures containing divanadium pentaoxide
- Stigmatisation of articles containing vanadium substances, even if they are bound in a matrix and thus not biologically available
- Changes to labelling, packaging and eSDS
- Additional investment and/or equipment costs
- Additional RMMs required
- Possibility for a future authorisation or restriction under REACH affecting vanadium-containing frits
- Possible precedent setting for classification outside the EU
- Impact on other related legislation (e.g. waste, occupational health and safety legislation, etc)
- Impact for other raw materials where divanadium pentaoxide may be present as an impurity
All the above would result on an increase of operational costs and loss of competitiveness face to our competitors in the rest of the world and may trigger delocalisation.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Contribution V2O5 CLH Public Consultation_FC.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Spain	Inorganic Pigments Consortium	Industry or trade association	3

Comment received

The Inorganic Pigments Consortium is the organization that manages the REACH and CLP obligations of companies that manufacture or import inorganic pigments into the EU. The Consortium currently includes 25 members from different European countries, mainly Spain, Italy, Germany and UK. The members of the IP Consortium are the largest producers in Europe for inorganic pigments.
Complex inorganic pigments are chemical substances manufactured by means of an industrial process, which involves a chemical reaction. In this process, a mixture of raw materials (typically consisting of metal oxides and salts) undergoes a calcination reaction at high temperatures forming a specific crystalline matrix. Divanadium pentaoxide is a key raw material for the manufacture of some specific complex inorganic pigments to obtain certain colour ranges and cannot be substituted. During the pigment manufacturing process, raw materials are transformed via calcination and the resulting inorganic pigments contain vanadium ions bound to the crystalline structure. These substances are exclusively manufactured at industrial sites by trained workers and their main end uses are ceramics, metals, plastics and paints or coatings.

The Inorganic Pigments Consortium fully supports the scientific and technical position of the Vanadium REACH Consortium in relation to the current Public Consultation to modify the existing entry for divanadium pentaoxide in Annex VI of the CLP Regulation.

Impact of the CLH proposal in our sector :
The proposed harmonised classification and labelling for divanadium pentaoxide would have a negative impact in our sector mainly due to its use as raw material, but also due to potential stigmatisation of vanadium-containing pigments, even if scientific information show that vanadium ions are not released from the crystalline structure of pigments and therefore not bioavailable.
The following main consequences have been identified:
- Changes in the manufacturing and handling practices
- Market impact due to stigmatisation of all substances and mixtures containing vanadium compounds
- Stigmatisation of articles containing vanadium-containing pigments, even if their constituents are bound in a matrix and thus not biologically available.
- Changes to labelling, packaging and eSDS
- Additional investment and/or equipment costs
- Additional RMMs required
- Possibility for a future authorisation or restriction under REACH affecting vanadium-containing pigments
- Possible precedent setting for classification outside the EU
- Impact on other related legislation (e.g. waste, occupational health and safety legislation, etc)
- Impact for other raw materials where divanadium pentaoxide may be present as an impurity
All the above would result on an increase of operational costs and loss of competitiveness face to our competitors in the rest of the world and may trigger delocalisation.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Contribution V2O5 CLH Public Consultation_IPC.pdf

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	United States		Individual	4
Comment received				
Throughout the CLH report insufficient consideration is give to the complex nature of vanadium chemistry so that information has been included in the assessment that is not relevant to divanadium pentaoxide. See attachment: CLH-V2O5 chemistry comments by David White-2019-11-21.pdf ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH-V2O5 chemistry comments by David White-2019-11-21.pdf				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	5
Comment received				
The French MSCA proposes to add classification as Carc. 1B (H350) to the Annex VI entry.				

The proposal is based on two reliable 2-year carcinogenicity tests with mice and rats exposed to V2O5 via inhalation. Increased incidences of tumours (alveolar, bronchiolar neoplasms: adenoma and carcinoma) without excessive toxicity at test doses in male and female B6C3F1 mice were shown. Some evidence of carcinogenic activity in male F344/N rats was observed (NTP, 2002). In addition to these results, V2O5 exposure significantly promoted lung tumours (solid adenomas) in A/J and BALB/cJ mice (Rondini et al., 2010). No human data with positive association between cancer and exposure to V2O5 is available.

In a weight of evidence approach and considering additional important factors to assess the overall level of concern (tumour type and background incidence, progression of lesions to malignancy, reduced tumour latency, responses in male and female mice, route of exposure, no excessive toxicity) V2O5 is presumed to have carcinogenic potential for humans. We agree that classification as Carc. 1B (H350) would be justified.

However, there are also arguments for a classification in category Carc. 2. Dose dependent effects (alveolar/ bronchiolar carcinoma or adenoma) were only observed in one species (B6C3F1 mice) with the lung as the only site of response. Moreover, in historical controls (NTP historical controls report) the overall incidence of alveolar/ bronchiolar carcinoma or adenoma in lung is high (about 32 %). These arguments should be included in the discussion regarding the classification of V2O5 in Carc. 1B or Carc. 2.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany	Vanadium Consortium / Vanitec	Industry or trade association	6

Comment received

Carcinogenicity:
In the view of the Registrant, the NTP (2002) inhalation study in rats and mice does not provide sufficient data to draw definitive conclusions regarding thresholds and/or mechanisms of action or mode of action. The relevance of the lung tumours in mice is severely confounded by the chronic and persistent inflammation, presumed to have occurred over the whole duration of the two-year exposure, and the lack of a dose-response relationship.
Divanadium pentaoxide reacts strongly acidic, so that this is likely to contribute to the chronic inflammation. Further, V2O5 is not expressing its carcinogenic activity via genotoxicity since tumours did not develop at other organ sites following 2-years of inhalation even though divanadium pentaoxide circulated systemically. Based on the absence of genotoxicity, divanadium pentaoxide is thought to exert genotoxicity by indirect mechanisms (secondary genotoxicity, i.e. chronic inflammation and oxidative stress).
The tumour promoting activity in mice, although strain-dependent (Rondini et al., 2010) may be considered part of that mode of action of V2O5. It is further noted that there is a high degree of discordance between rats and mice in the development of chemically induced lung tumours, as shown in a statistical analysis of 58 compounds tested in NTP two-year inhalation studies (Smith & Anderson, 2017). From this data, it has also been concluded that bronchioalveolar lung tumours induced only in mice by non-genotoxic chemicals are of low relevance for human lung cancer risk (Smith et al., 2018). Further, the genomic responses of mice to inflammation are of questionable comparability to those of humans (Seok et al., 2013).
Finally, the available carcinogenicity data relate only to inhalation exposure of rats and mice to divanadium pentaoxide, which affected only the respiratory tract, and with

tumour formation only in mice lungs which is considered a substance-specific local effect. The NTP (2002) study does not report any treatment related lesions in other tissues whatsoever, despite measured vanadium levels in blood indicating systemic exposure. In conclusion, the evidence of carcinogenicity in mice of both sexes (NTP, 2002) is not considered sufficient for classification of divanadium pentaoxide as a Category 1B substance. Instead, a classification in Category 2 – H351i appears to be most appropriate and adequately conservative. Additionally, any classification should be route-specific, i.e. restricted to inhalation.

Please refer for a detailed argumentation to the attachment "Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	United Kingdom		Individual	7
Comment received				
see Public Attachment: Comments on CLH carcinogenicity-Len Levy-2019-11-20.pdf see pages 50-62 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH carcinogenicity-Len Levy-2019-11-20.pdf (2).pdf				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	8
Comment received				
The French MSCA proposes to change the current Annex VI entry from Muta. 2 (H341) to Muta. 1B (H340). The DS states that there is no heritable germ cell mutagenicity test in mammals performed by physiological route but refers to a positive dominant lethal test (Altamirano-Lozano et al., 1996) performed with intraperitoneal injection. However, the reliability of this test is questionable, because concurrent positive controls, which "should always be used unless the laboratory has demonstrated proficiency" (OECD TG 478), were not included in this test. Laboratory proficiency is not given. A firm assessment of results is thus questionable. No other in vivo heritable germ cell mutagenicity test in mammals judged to be reliable is available in the dossier. Available in vivo somatic cell mutagenicity tests in mammals in the dossier, which were judged to be reliable (Klimisch 1 or 2) by the DS (in vivo micronucleus assays by Anonymous 2001 and NTP 2002) are negative. These tests were performed using physiological routes (inhalation, oral). All available positive in vivo somatic cell tests (two comet assays) considered to be reliable by the DS are genotoxicity (indicator) tests and are performed by the intraperitoneal route.				

Thus, the criteria for classification as Muta 1B are not fulfilled.

Moreover, all in vivo mutagenicity/genotoxicity tests judged to be reliable by the DS with positive results (Altamirano-Lozano et al., 1996; Altamirano-Lozano et al., 1999) used the intraperitoneal exposure route. All in vivo tests using oral and inhalation exposure judged to be reliable by the DS (micronucleus assays by Anonymous 2001, NTP 2002, Comet assay by Schuler 2011) are negative. According to Guidance on the Application of the CLP criteria (2017): "In summary, classification as a Category 2 mutagen would generally apply if only intraperitoneal in vivo tests show mutagenicity/genotoxicity and the negative test results from the in vivo tests using other routes of application are plausible."
The negative test results from the in vivo tests using other routes of application (inhalation, oral) are plausible (tests considered valid) and only intraperitoneal in vivo tests show mutagenicity/genotoxicity.
According to the Guidance on the Application of the CLP Criteria, classification of Cat. 2 would apply in this case.
The DS states on p. 49 that "In addition to the positive dominant lethal assay performed by intraperitoneal route, in vivo micronucleus assays and Comet assays in somatic cells are positive after respiratory exposure", however, all these tests were judged to be not reliable (Klimisch 3, Klimisch 4) by the DS and should be disregarded from a firm assessment of the data. All in vivo mutagenicity/genotoxicity tests applying physiological routes considered reliable by DS were negative.

All in all, the DE CA does not support to change the current Annex VI entry from Muta. 2 (H341) to Muta. 1B (H340).

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	United States		Individual	9

Comment received

The Muta 1B classification is neither warranted nor justified for V2O5.

In the most stringent and relevant in vivo genotoxicity studies in which the genotoxicity of V2O5 was investigated using high, tumorigenic concentrations, no evidence for either mutagenicity or chromosomal damage or aneugenicity was shown. These studies include Manjanatha et al. (2015), Banda et al. (2015), Black et al. (2015), Schuler et al. (2011) and NTP (2002). A number of other studies claimed positive findings for in vivo genotoxicity. In general, several of these latter studies suffer from methodological issues. The important question to ask in this context is whether to give any weight to these deficient studies, especially when much higher quality studies are already available from which to make an independent assessment. In the opinion of this reviewer, given the preponderance of weight available from those studies that either followed a validated protocol or were conducted according to the state-of-the-art methodology, it is reasonable to conclude that V2O5 is not likely to be an in vivo genotoxicant. Consequently, the Muta 1B classification is neither warranted nor justified. In this case, the most appropriate, worst-case scenario, classification for V2O5 is Category 2.

This review's conclusion that V2O5 is not likely an in vivo genotoxicant strengthens the argument that this substance is not a genotoxic carcinogen and DNA reactivity can be excluded in the mode of action for mouse lung tumours. This conclusion was based on the absence of genotoxicity in the tumour target tissue (i.e., lung) using multiple, well-established endpoints.

This information is further expounded upon in the attached report.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH mutagenicity-comments by Gollapudi Bhaskar-2019-11-21.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany	Vanadium Consortium / Vanitec	Industry or trade association	10

Comment received

Lack of evidence of a primary genotoxic mechanism of action for divanadium pentaoxide:
The analysis of the available data as employed in the CLH report does not appear to transparently weigh the relevance, reliability and adequacy of the data sources. The selection of the studies to be compared against the CLP criteria remains unclear and unexplained, so that the decision on the classification lacks transparency.
The Registrant has undertaken a thorough evaluation of all available data and has compared the data against the classification criteria as laid down in the Guidance on the Application of the CLP criteria (ECHA, 2017) in a weight-of-evidence analysis. A detailed analysis is presented in chapter 2.5 below. The outcome of this weight-of-evidence analysis can be summarised as follows:
• No evidence for in vitro mutagenicity in bacteria
• Equivocal evidence for in vitro clastogenicity/aneugenicity
• No evidence for in vitro mutagenicity in mammalian cells
• No evidence for in vivo mutagenicity in transgenic rodents
• No evidence for site of in vivo contact genotoxicity after inhalation
• No evidence for in vivo clastogenicity, positive findings stem largely from unreliable studies with unphysiological route of exposure
• Positive findings were largely obtained from studies published by one and the same working group of E. Rojas and M. A. Altamirano-Lozano (University of Mexico City), whose study design and reporting shows recurring deficiencies
In contrast to the CLH report, the Registrant finds that the genetic toxicity studies actually support the conclusion that divanadium pentaoxide does not elicit any mutagenic activity.
The weight-of-evidence analysis of the entire genotoxicity database does not show any clear evidence of germ cell mutagenicity. Consequently, divanadium pentaoxide should not be classified in Category 1B. On the basis of the information obtained from relevant and reliable studies but also considering the remaining studies with all their limitations, the current classification with "Mutagenicity Category 2 – H341" already appears overtly conservative.

Please refer for a more detailed argumentation to the attachment "Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number

22.11.2019	Germany	Vanadium Consortium / Vanitec	Industry or trade association	11
Comment received				
Effects on fertility and effects via lactation: The Registrant contends that taking the information from several publications together, there is only limited and weak evidence from these studies that divanadium pentaoxide exposure by the inhalation and oral route may affect male and female fertility. This evidence is not considered strong enough to support classification in Cat 1B. It is therefore proposed to retain the already existing Category 2 – H361f. For adverse effects on development, the Registrant is of the opinion that the current harmonised classification with Repro. Category 2 H361d for development is still justified and should be retained. This is supported by the available information on developmental toxicity. For adverse effects on or via lactation, the publications referred to by the CLH report are all of low reliability (RL=3) , but the CLH report nevertheless comes to the conclusion that classification as H362: May cause harm to breast-fed children is warranted. This conclusion is derived from a limited data set without taking relevant uptake routes into consideration; however, an appropriate assessment is not possible due to a lack of any reported (no) effect level. The data summarised by the DS are not considered to represent clear evidence of adverse effects in the offspring due to transfer in the milk or adverse effect on the quality of the milk. There are also no reliable data that indicate the likelihood that the substance is present in potentially toxic levels in breast milk. Overall, the available data do not justify classification for lactation effects. In a very recent publication by US NTP, three-month toxicity studies of tetravalent and pentavalent vanadium compounds in Hsd:Sprague Dawley SD rats and B6C3F1/N mice via drinking water exposure are described (Roberts et al. 2019). Data on the number of offspring from treatments, post implantation in utero and live births, birth weights, and weight gains were generated. The results for vanadium in its pentavalent form indicate that fetal effects are only seen at levels that are toxic to mothers, so that vanadate ions do not appear to be selectively affecting live births or to be selectively toxic to neonates. The full findings of these sub-chronic studies are not available yet, but are expected to be published in 2020. They can reasonably be expected to provide valuable information regarding conclusions on the effect of vanadium in its pentavalent form on fertility and effects via lactation, thereby closing a data gap. Since the Registrant has been aware of these studies, a testing proposal was previously not submitted in the REACH registration of divanadium pentaoxide to avoid duplicate animal testing. The Registrant suggests that any decision on the classification for effects of divanadium pentaoxide on reproduction and via lactation should be deferred until the full study reports will be available for rats and mice. Please refer for a detailed argumentation to the attachment "Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf". ECHA note – An attachment was submitted with the comment above. Refer to public attachment Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	12
Comment received				
The French MSCA proposes to change the current Annex VI entry from Repr. 2 (H361d***) to Repr. 1B (H360Fd) and to add Lact. (H362).				

The proposal for the fertility classification is predominantly based on adverse effects on the male reproductive system, such as impaired sperm motility in mice after inhalation (NTP, 2002), atrophy of the secondary reproductive organs, hypospermia of the testis and atypical cells of the epididymis in rats after 90 days inhalation (NTP, 2002). These effects have been associated with marked body weight loss and general debilitation. Adverse effects on male fertility have been observed in several other studies in the absence of overt toxicity signs or weight change (e.g., Fortoul et al., 2007: necrosis of spermatogonia, spermatocytes and Sertoli cells). Similar adverse effects on testes and sperm were observed for ammonium metavanadate and sodium metavanadate. With respect to the specific adverse effects on male reproductive organs originating from several studies, fertility classification as Repr. 1B (H360F) is justified.

Developmental effects, such as delayed ossification, reduced foetal body weight, increased foetal mortality have been documented in several studies, all of which have methodological shortcomings and are hence not regarded as reliable. Since most effects have been observed consistently in the different studies, we agree that classification as Repr. Cat. 2 for development is justified.

The French MSCA proposes to add classification as H362: May cause harm to breast-fed children in Annex VI. No studies with V2O5 are available which evaluate effects on or via lactation. This proposal is based on five studies with sodium metavanadate (NaVO3, post-natal i.p. injection) and one study with Pentavanadate (not further specified). However, all studies are limited in study design (e.g., only one dose level) and/or in reporting (e.g., no purity information) resulting in Klimisch score 3. Due to qualitative limitations, results of one of these studies would not be sufficient to conclude adverse effects on or via lactation. However, consistent neurotoxic effects demonstrated in these studies (e.g., demyelination in two studies and astrogliosis in three studies) make the conclusion of effects via lactation credible in a weight of evidence approach. Additionally, a read across justification has been provided by the dossier submitter demonstrating that read-across from sodium metavanadate to V2O5 is justified (e.g., because V2O5 releases the same vanadium ions as sodium metavanadate in water or body fluids and bioaccessibility studies indicate comparable absorption rates). Moreover, similar neurotoxic effects of the target substance V2O5 observed in adult animals support the read-across and the neurotoxic potential of V2O5. Therefore, we agree with classification as H362: May cause harm to breast-fed children.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	13
Comment received				
No potential for respiratory sensitisation was found for V2O5 in one sub-chronic inhalation study with monkeys (Knecht et al., 1992) and in four case-control studies with workers from vanadium processing industries. Thus, we agree that no classification is required for this endpoint.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany	Vanadium Consortium / Vanitec	Industry or trade association	14

Comment received
Acute toxicity via the oral route: The DS has selected an LD50 using the findings of an acute oral study in female rats with a pulverised product of technical grade (Leuschner, 1991a), thereby disregarding data available both for the pure substance, i.e. pulverised, analytical grade (Leuschner, 1991c) or the technical fused product as marketed (Leuschner, 1991b). The Registrant contends that for the assessment of the true intrinsic toxicity of a substance, the results of the oral toxicity of the pulverised "pure" analytical grade in female rats are more relevant and appropriate. Thus, based on the study by Leuschner (1991c), divanadium pentaoxide is already conservatively classified as Acute Oral Toxicity Category 4 – H302. This existing classification should be retained. Acute toxicity via inhalation: In his classification proposal, the DS has chosen an unusual approach in deriving an LC50 by using only one gender-specific finding in only one acute inhalation study in mice, thereby disregarding reliable data for male mice in the same study (Sullivan, 2011a). This sex-specific derivation is not considered reasonable and is not in accordance with OECD guideline 436, since both male and female animals were tested and therefore results of both sexes should be pooled together. In contrast, in the opinion of the Registrant the acute toxicity findings obtained in rats supported by further findings in mice (Sullivan 2011a,b) document that very fine divanadium pentaoxide powder should instead be classified as: Acute Inhalation Toxicity Category 2 "Fatal if inhaled" – H330". However, the above mentioned very fine divanadium pentaoxide powder was artificially generated in a laboratory by milling, whereas commercially available grades are far coarser (<3% of particles (w/w) < 10 µm). In the studies by Sullivan (2011a,b), granular divanadium pentaoxide was milled to produce a very fine powder (>96% of particles (w/w) < 10 µm) to conduct the inhalation exposures in rodents for comparative research purposes. These tests were not carried out with the substance in the form in which it is placed on the market and in which it can reasonably be expected to be used. According to the CLP Regulation Article 9(5), "when evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used." Thus, based on the study by Leuschner (1991d,e,f), divanadium pentaoxide in the forms in which it is actually placed on the market and is used, is already adequately and conservatively classified as Acute Inhalation Toxicity Category 4 – H332. The existing classification should be retained. Please refer for a more detailed argumentation to the attachment "Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf". ECHA note – An attachment was submitted with the comment above. Refer to public attachment Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	15
Comment received				
The French MSCA proposes to change the current Annex VI entry from Acute Tox. 4* (H332, H302) to Acute Tox. 1 (H330) and Acute Tox. 3 (H301). The proposal for the Acute Tox. oral classification (Cat. 3, H301) is based on eight of the twelve available studies resulting in an LD50 between 50-300 mg/kg bw, resulting in				

Acute toxicity hazard Category 3. The two studies resulting in LD50 < 50 mg/kg bw are considered not assignable (Klimisch score 4, Izmerov et al. 1982, mouse, 23 mg/kg bw) or not reliable (Klimisch score 3, Massmann, 1956, rat, LD50: 10.4 mg/kg bw) due to insufficient details on the protocol and substance tested. Therefore, we agree that Acute Tox. 3 – H301 is warranted and that an ATE of 100 mg/kg bw should be applied.
The proposal for the Acute Tox. inhalation classification (Cat. 1, H330) is based on one study resulting in an LC50 for female mice of <0.056 mg/l (Anonymous 2011, lethality females: 2/3 and 3/3 at 0.056 and 0.5 mg/l respectively, Klimisch score 2), which is (practically) below the threshold for Acute Tox. 1 classification (≤0.05 mg/l). Five more acute tox. inhalation toxicity studies with rats are available resulting in LC50 ≥ 0.25 mg/l, indicating that rats are less sensitive than mice. One study with rabbits is available with LC50 = 0.205 mg/l. Since classification should be based on the lowest LC50 value available, we agree that classification as Acute Tox. 1 – H330 and an ATE of 0.005 mg/l are warranted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	16
Comment received				
The French MSCA proposes to update the current Annex VI entry from STOT RE 1 (H372**) to STOT RE 1 (H372 (respiratory tract, inhalation)) to include the target organ and the route of exposure. We agree that the current harmonized classification is still justified based on the available studies but that an update is warranted.				

PUBLIC ATTACHMENTS
1. Vanadium Consortium-Vanitec_Comments on CLH proposal of V2O5_2019-11-22.pdf [Please refer to comment No. 1, 6, 10, 11, 14]
2. Contribution V2O5 CLH Public Consultation_FC.pdf [Please refer to comment No. 2]
3. Contribution V2O5 CLH Public Consultation_IPC.pdf [Please refer to comment No. 3]
4. CLH-V2O5 chemistry comments by David White-2019-11-21.pdf [Please refer to comment No. 4]
5. CLH mutagenicity-comments by Gollapudi Bhaskar-2019-11-21.pdf [Please refer to comment No. 9]
6. Comments on CLH carcinogenicity-Len Levy-2019-11-20.pdf (2).pdf [Please refer to comment No. 7]