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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Last data extracted on 23.08.2019

Substance name: tellurium dioxide
CAS number: 7446-07-3
EC number: 231-193-1
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2019	Belgium	European Special Glass Association	Industry or trade association	1
Comment received				
Tellurium oxide is an indispensable element for the synthesis of special optical filter glass with functioning coloring in higher edge layers.				

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2019	Canada	<confidential>	Company-Manufacturer	2
Comment received				
These comments are submitted on behalf of both <confidential> and <confidential>. - Section 9.2.5.1. Read-across justification based on in silico data Table 9 of Te CLH report and Table 10 of TeO2 CLH Report on "OECD QSAR Toolbox profiling" / Cramer Scheme: <confidential> and <confidential> argue against the use of the Toxic hazard classification by Cramer (indicated as "high (class III)") for both tellurium and tellurium dioxide. In Lapenna and Worth, 2011, Analysis of the Cramer classification scheme for oral systemic toxicity - implications for its implementation in Toxtree, EUR 24898 EN, page 2, it is explicitly written "The tree is intended for use with all ingested, structurally defined organic and metallo-organic substances." Tellurium and tellurium dioxide are neither organic nor metallo-organic substances. - Section 1.1 Name and other identifiers of the substance • <confidential> and <confidential> confirm that they do not market tellurium or tellurium dioxide as nano scale products.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2019	Germany		MemberState	3
Comment received				
The read across between tellurium dioxide and tellurium for the endpoints germ cell muta-genicity and reproductive toxicity is well justified. The read across justification is				

based on identical metabolites in vivo, very similar physico-chemical properties and a high degree of concordance for the toxicological properties of both substances.

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	4
Comment received				
- Section 9.2.5.1. Read-across justification based on in silico data Table 9 of Te CLH report and Table 10 of TeO2 CLH Report on "OECD QSAR Toolbox profiling" / Cramer Scheme: The Consortium argues against the use of the Toxic hazard classification by Cramer (indicated as "high (class III)") for both tellurium and tellurium dioxide. In Lapenna and Worth, 2011, Analysis of the Cramer classification scheme for oral systemic toxicity - implications for its implementation in Toxtree, EUR 24898 EN, page 2, it is explicitly written "The tree is intended for use with all ingested, structurally defined organic and metallo-organic substances." Tellurium and tellurium dioxide are neither organic nor metallo-organic substances. - Section 1.1 Name and other identifiers of the substance The members of the Consortium confirm that they do not market tellurium or tellurium dioxide as nano scale products. ECHA note – An attachment was submitted with the comment above. Refer to public attachment tellurium dioxide.pdf				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2019	Canada	<confidential>	Company-Manufacturer	5
Comment received				
<confidential> and <confidential> supports the "no classification" conclusion for ththis hazard class for tellurium dioxide.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2019	Germany		MemberState	6
Comment received				
Based on the available data the proposal for no classification is supported. The available data shows negative results for bacterial reverse mutation assay (OECD TG 471), in vitro mammalian cell gene mutation test (OECD TG 476) and in vitro mammalian chromosome aberration test (OECD TG 473).				

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	7
Comment received				
Mutagenicity and Carcinogenicity				

The Consortium supports the "no classification" conclusion for these two endpoints for the two substances.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment tellurium dioxide.pdf

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2019	Canada	<confidential>	Company-Manufacturer	8

Comment received

a. Developmental toxicity (Repro 1B, H360D):

<confidential> and <confidential> supports the classification as Repro 1B, H360D. This classification has been provided in the registration dossiers for tellurium and tellurium dioxide and implemented in the Safety Data Sheets for these substances.

b. Adverse effects on sexual function and fertility (Repro 1B, H360F):
<confidential> and <confidential> based the below on a recent third-party expert toxicologist review.

Our interpretation is to differentiate effects on fertility (= up to implantation) from developmental effects (fetal and beyond).

CLH report Section 10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

OECD TG 421 – Arguments against maternal toxicity at the MD (120 mg/kg bw/day)
In the CLH report, it is indicated that "gestation index and gestation length were also observed at doses (MD), which did not cause severe toxicity. Further, the marked effects on the structure of the female reproductive organs are also considered to be substance related and not secondary to maternal toxicity".

However, no abnormalities, apart from hepatotoxicity, were observed in the histopathological analysis of the MD group (the ovary appeared to be normal).

Table extracted from the TG 421 full study report (page 92) and provided to the Dutch authorities.

Furthermore, in this MD group, the "fertility ss" parameters (pre-mating, mating and implantation) are not significantly (in the statistical sense) different from the controls. The deviation is minimal (+/- 5 %) and could be due to biological variation.

Table extracted form the TG 421 full study report (page 36) - provided to the Dutch authorities.

The reduced gestation index can be explained due to developmental effects (4/12 dams had still-born pups, so categorized un foetal toxicity and not fertility).

OECD TG 421 – Arguments against maternal toxicity being a secondary effect of systemic toxicity at the HD (600 mg/kg bw/day)

Even if the following statement 'The reproductive organ effects in females are not

considered to be secondary effects of systemic toxicity.' is rightly reported in the CLH reports to be in the executive summary of the registration dossiers, a recent third-party toxicologist expert judgement challenged this interpretation with the following arguments:

- A motivation for this statement is lacking, considering it is known that already mild food deprivation can affect the estrous cycle of rats.
- Several clinical signs of toxicity (intestinal, hepatic and mesenteric lymph node toxicity, with some effects in kidney and thymus, and pigment deposits in a number of affected tissues) were noted which could provide explanations for the effects on reproductive organ as secondary effects
- The histopathological evaluation was only performed on 2 rats (available) for the HD group while in all other groups at least 10 animals were evaluated per group.
- In the report of the pathological evaluation (appendix 3- based on only 6 animals, see below table), ovarian atrophy was observed in 4 (1 minimal and 3 mild) of the 6 animals (with no distinction between the pregnant / non-pregnant animals). There is no description of the observed ovarian 'atrophy' (eg follicle size distribution, atresia of primordial follicles, ….). This makes it impossible to judge whether exposure to tellurium / tellurium dioxide might cause primary effect on the ovary.

Based on this information, our interpretation is that there are no arguments to overrule the secondary effects due to overt toxicity and assign primary reproductive toxicity at the HD group. The effects noted on the uterus and vagina are (probably) due to the inactivity of the ovary (so a secondary effect).

Table extracted from the TG 421 full study report (page 261 – Appendix 3 – Pathology evaluation) - provided to the Dutch authorities.

We agree with the statement in the CLH report that "Whether the effects on reproduction observed in the screening study are (partially) secondary to general toxicity is a matter of discussion".

We contend, based on the above, that effects observed on tellurium and tellurium dioxide are not enough so that the substances are classified as H306 F Cat. 1B.

As the primary data from the TG 421 full study report do not provide evidence that such effects on female reproductive organs cannot be unequivocally considered NOT to be secondary non-specific consequence of the other toxic effects, we recommend no classification for the fertility.

We therefore contend that for the reproductive toxicity, only developmental effects should be taken into consideration, with a H360 D, Cat. 1B classification.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2019	Germany		MemberState	9
Comment received				
1. Fertility The classification of tellurium dioxide as Repr. 1B, H360F, is not supported. The proposal is based on effects observed in an OECD 421 Screening study (NN, 2013) in rats orally exposed to tellurium dioxide. The effects are a decrease of the fertility-, mating- and gestation index of females in the highest dose group (600 mg TeO2/kg bw/d). However, at this dose 5 out of 12 females died during the experiment, corresponding to 40 % of the animals. The increased mortality indicates a severe toxicity of the substance. According to the guidance, effects as-sociated with such severe toxicity should not be included in the				

evaluation:

Annex I: 3.7.2.4.4.
"Maternal mortality:
An increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related man-ner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation. "

Maternal toxicity is further demonstrated by the reduced body weight of 18 % (MD) and 30 % (HD) below controls.

Under consideration of the very specific and uncommon nature of effects observed in the OECD TG 421 study (e.g., atrophy of ovary, uterus, and/or vagina) plus similar effects ob-served in an OECD TG 407 study at 600 mg/kg bw/d (TeO2, rat, oral, study report, 2013: epi-thelial atrophy of the vagina in 2 of 4 HD females, mortality 1) we agree with NL and the authors of the OECD TG 421 study report, that the reproductive organ effects in females are most likely not secondary effects of systemic toxicity. Additionally, histopathology of repro-ductive organs has only been performed for HD and control animals and thus potential simi-lar effects on the reproductive organs in the MD group could have been unnoticed. Further-more, effects on gestation index and gestation length were also observed at doses (MD), which did not cause mortality.

Taking into account the uncertainties resulting from the severe toxicity of tellurium in the high dose of the TG 421 study, the German CA considers the observed reproductive effects in the MD as consistent to effects in the HD - also accounting for vaginal atrophy in surviving animals of the TG 407 study - to support a classification as Repr. 2, H361f.

2. Developmental toxicity
The classification proposal of tellurium dioxide as Repr. 1B, H360D is supported.
There are two prenatal developmental toxicity studies (Johnson et al., 1988) conducted in rat and rabbit, respectively and five supporting studies in rats. The studies were performed with tellurium and the read across substance tellurium dioxide. In all of the studies on rats and rabbits severe effects on the development of the foetuses were observed. For both, rats and rabbits, severe malformations such as hydrocephali were found after administration of tellurium resp. tellurium dioxide. Hydrocephali have also been identified in supportive stud-ies in rats. In addition, in rats a greatly increased fetal mortality was observed. Maternal toxicity can be considered as low, as feed intake and weight gain was only slightly reduced and no mortality of the dams were observed. Accordingly, malformations and increased fetal mortality in rats may result from exposure to tellurium or tellurium dioxide and is not considered a secondary effect.

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	10
Comment received				
Reproductive toxicity: a. Developmental toxicity (Repro 1B, H360D):				

The consortium agrees with the classification Repro 1B, H360D. This classification is consistent with the self-classification provided in the dossiers for tellurium and tellurium dioxide and implemented in the Safety Data Sheets for these substances.

b. Adverse effects on sexual function and fertility (Repro 1B, H360F):

The Consortium based the below on a recent third-party expert toxicologist review.

Our interpretation is to differentiate effects on fertility (= up to implantation) from developmental effects (fetal and beyond).

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PUBLIC ATTACHMENTS
1. tellurium dioxide.pdf [Please refer to comment No. 4, 7, 10]