

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

CAS number: 13494-80-9

EC number: 236-813-4

Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	1

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.

- Section 5: Identified Uses (of tellurium)

The Consortium confirms that tellurium metal is used as an alloying element e.g. in steel and copper. However, we disagree with the written sentence below: "Tellurium alloys, especially cadmium-tellurium alloys form a compound that exhibits enhanced electrical conductivity." Cadmium telluride is in fact a substance according to REACH Regulation with following identifiers (EC 215-149-9 and CAS 1306-25-8) and has been registered accordingly. The use of tellurium to manufacture CdTe is consequently a use as 'intermediate' and not an alloying use.

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

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2019	Germany	<confidential>	Company-Manufacturer	2

Comment received

The below comments represent the comments from both <confidential> and <confidential> legal entities.

- Section 9.2.5.1. Read-across justification based on in silico data
Table 9 of Te 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.

- Section 5: Identified Uses (of tellurium)
<confidential> and <confidential> confirm that tellurium metal is used as an alloying element e.g. in steel and copper. However, we disagree with the written sentence below: "Tellurium alloys, especially cadmium-tellurium alloys form a compound that exhibits enhanced electrical conductivity." Cadmium telluride is in fact a substance according to REACH Regulation with following identifiers (EC 215-149-9 and CAS 1306-25-8) and has been registered accordingly by <confidential>. The use of tellurium to manufacture CdTe is consequently a use as 'intermediate' and not an alloying use.

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
13.08.2019	Belgium	European Special Glass Association	Company-Manufacturer	4
Comment received				
Te is used in the synthesis of glasses belonging to the group of chalcogenide glasses which have superior thermo-mechanical properties, displaying a low melting temperature with the exclusion of oxygen, allowing them to be shaped into optical devices such as lenses and optical fibers. These glasses are needed for electron conductive glasses and are used for transparency in infrared radiation, due to their higher atomic masses and smaller bonding force constants which lead to lower vibration absorption frequencies.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	5

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.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2019	Germany	<confidential>	Company-Manufacturer	6
Comment received				
<confidential> and <confidential> supports the "no classification" conclusion for this hazard class for the two substances.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2019	Germany		MemberState	7
Comment received				
All mutagenicity assays applied for source and target substances were negative (OECD TG 471 for tellurium and tellurium dioxide, OECD TG 473 for tellurium dioxide, OECD TG 476 for tellurium dioxide). Thus, there is no evidence that the substance has the potential to cause germ cell mutations. The proposal for no classification is supported.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2019	Germany	REACH Selenium & Tellurium Consortium	Industry or trade association	8
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).				
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): see attachment.

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 from the TG 421 full study report (page 36): see attachment.

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’ (e.g. 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) : see attachment.

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.

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

Date	Country	Organisation	Type of Organisation	Comment number
02.08.2019	Finland		MemberState	9

Comment received

Reproductive and developmental effects of tellurium have been investigated in a number of in vivo studies. In a reliable read-across reproductive screening study carried out with tellurium dioxide, reduced mating and fertility indices and a reduced gestation index were observed in rats at the high dose, which also induced mortality and systemic toxicity. 4 of 6 high-dose females were non-pregnant, and decreased or no corpora lutea and no implantation sites were noted in them at necropsy. Atrophy of reproductive organs was observed in all females at the high dose. Reduced gestation index and gestation length were also observed at middle dose, which did not cause severe toxicity. Tellurium had no effects on male reproductive system in the study.

In a reliable developmental toxicity study, hydrocephalus was the major malformation in rats accompanied by increased pup mortality at the highest dose level. These effects occurred at doses that elicited only slight toxicity in dams. In a similar study in rabbits, decreased fetal body weights, increased incidence of variations, delays in ossification and hydrocephali were observed. Several other developmental studies, although with limitations, consistently describe induction of hydrocephalus in rats. Since there is no evidence on species specificity, this effect can be considered as relevant to humans.

Mechanistic data suggests that tellurium may interfere with the endocrine system by inhibiting squalene epoxidase, an enzyme participating in the synthesis of cholesterol, which is the precursor of steroid hormones. This may be a possible, although not verified, explanation for the observed disturbances of the oestrous cycle in the reproductive screening study. Maternal mortality in the same study was excessive at the high dose, and it cannot be excluded that some of the observed adverse effects are secondary to maternal toxicity. Structural effects like reproductive organ atrophy and influence on number of corpora lutea and oestrus cycle can still be regarded as substance-related. Moreover, effects on reproduction were also noted at the middle dose where no severe toxicity was present. Developmental toxicity (hydrocephali) was observed in all reported studies on tellurium or the read-across substance tellurium dioxide.

There are no human data available addressing adverse effects of tellurium on reproductive system or development. Based on the available information and the classification criteria, FI CA supports the proposed classification of tellurium as Repr. Cat. 1B; H360FD.

Date	Country	Organisation	Type of Organisation	Comment number
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15.08.2019	Germany	<confidential>	Company-Manufacturer	10
Comment received				
<p>a. Developmental toxicity (Repro 1B, H360D):</p> <p><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.</p> <p>b. Adverse effects on sexual function and fertility (Repro 1B, H360F):</p> <p><confidential> and <confidential> based the below on a recent third-party expert toxicologist review.</p> <p>Our interpretation is to differentiate effects on fertility (= up to implantation) from developmental effects (fetal and beyond).</p> <p>CLH report Section 10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility</p> <p>OECD TG 421 – Arguments against maternal toxicity at the MD (120 mg/kg bw/day)</p> <p>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”.</p> <p>However, no abnormalities, apart from hepatotoxicity, were observed in the histopathological analysis of the MD group (the ovary appeared to be normal).</p> <p>Table extracted from the TG 421 full study report (page 92) and provided to the Dutch authorities.</p> <p>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.</p> <p>Table extracted form the TG 421 full study report (page 36) - provided to the Dutch authorities.</p> <p>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).</p> <p>OECD TG 421 – Arguments against maternal toxicity being a secondary effect of systemic toxicity at the HD (600 mg/kg bw/day)</p> <p>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:</p> <ul style="list-style-type: none"> - 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	11

Comment received

1. Fertility

The classification of tellurium as Repr. 1B, H360F, is not supported. The proposal is based on effects observed in an OECD TG 421 screening study (NN, 2013) in rats orally exposed to read across substance tellurium dioxide. The effects are a decrease of the fertility- (63%, control 100%) and mating-index (73%, control 100%) of females in the highest dose group (HD, 600 mg TeO₂/kg bw/d), reduced gestation index in the mid-dose group (MD, 67%, control 92%) and HD group (0%), and atrophy of female reproductive tissues in the HD group. However, in the HD group 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 on the Application of the CLP Criteria, effects associated 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 manner

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 observed in an OECD TG 407 study at 600 mg/kg bw/d (tellurium dioxide, rat, oral, study re-report, 2013: epithelial atrophy of the vagina in 2 of 4 HD females, mortality 1) the German CA agrees 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 reproductive organs has only been performed for HD and control animals and thus potential similar effects on the reproductive organs in the MD group could have been unnoticed. Furthermore, 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 - and supports a classification as Repr. 2, H361f.

2. Developmental toxicity

The classification proposal of tellurium 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 and/or tellurium dioxide. Hydrocephali have also been identified in supportive studies 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.

PUBLIC ATTACHMENTS

1. tellurium.pdf [Please refer to comment No. 1, 5, 8]