**16. August 2019**

**Public consultation on harmonized classification proposal for tellurium**

**General comments**

- 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.

**Mutagenicity and Carcinogenicity**

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

**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.

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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)

TELLURIUM DIOXIDE: REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST FOLLOWING ORAL (GAVAGE) ADMINISTRATION IN WISTAR RATS

FEMALE: SUMMARY OF HISTOPATHOLOGICAL OBSERVATIONS

| Tissue / Observation | Necropsy | Pregnant | | | | Non-pregnant | Found dead $ | ≤ 5 implantation sites |
|---|---|---|---|---|---|---|---|---|
| Dose Group (mg/kg/day) | | Control | 25 mk/kg/day | 120 mg/kg/day | 600 mg/kg/day | 600 mg/kg/day | 600 mg/kg/day | Control |
| Number of animal examined | | 11 | 1 | 2 | 2 | 4 | 5 | 1 |
| **NO SIGNIFICANT FINDIGS** | | 10 | 0 | 0 | 0 | 0 | 0 | 1 |
| **LUNGS (All occurrences)** | | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| **Present animals** | | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Congestion, agonal, all lobes | **Total** | **0** | **0** | **0** | **0** | **0** | **2** | **0** |
| | Moderate | - | - | - | - | - | 2 | - |
| **LYMPH NODE, MESENTERIC (All occurrences)** | | 0 | 0 | 0 | 2 | 2 | 3 | 0 |
| **Present animals** | | 0 | 0 | 0 | 2 | 2 | 3 | 0 |
| Accumulation, pigmented macrophage, medulla | **Total** | **0** | **0** | **0** | **2** | **2** | **3** | **0** |
| | Minimal | - | - | - | 1 | - | 1 | - |
| | Moderate | - | - | - | - | 2 | 2 | - |
| | Mild | - | - | - | 1 | - | - | - |
| **OVARY (All occurrences)** | | 0 | 0 | 0 | 0 | 5 | 8 | 0 |
| **Present animals** | | | | | | 4 | 5 | |
| Atrophy, bilateral | **Total** | **0** | **0** | **0** | **0** | **4** | **2** | **0** |
| | Minimal | - | - | - | - | 1 | - | - |
| | Mild | - | - | - | - | 3 | 2 | - |
| Atrophy, left | **Total** | **0** | **0** | **0** | **0** | **0** | **2** | **0** |
| | Moderate | - | - | - | - | - | 2 | - |
| Atrophy, right | **Total** | **0** | **0** | **0** | **0** | **0** | **1** | **0** |
| | Minimal | - | - | - | - | - | 1 | - |
| Pigment deposit, blue/black, diffuse, right | **Total** | **0** | **0** | **0** | **0** | **0** | **1** | **0** |
| | Mild | - | - | - | - | - | 1 | - |
| Pigment deposit, blue/black, diffuse, bilateral | **Total** | **0** | **0** | **0** | **0** | **1** | **0** | **0** |
| | Mild | - | - | - | - | 1 | - | - |
| Vacuolation, corpora lutea, right | **Total** | **0** | **0** | **0** | **0** | **0** | **1** | **0** |
| | Moderate | - | - | - | - | - | 1 | - |

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)

| | Dose (mg/kg bw/day) | | | |
|---|---|---|---|---|
| | Control | 25 | 120 | 600 |
| Paired males - females | 12/12 | 12/12 | 12/12 | 11/12 |
| Mated males - females | 12/12 | 12/12 | 12/12 | 8/11 |
| Infertile males – Non-pregnant females | 0/12 | 0/12 | 0/12 | 3/11 |
| Pregnant females, but not delivered | 0/12 | 0/12 | 0/12 | 3/5 |
| Male-female Mating Index (%) | 100 | 100 | 100 | 73 |
| Male-female Fertility Index (%) | 100 | 100 | 100 | 63 |
| Gestation Index (%) | 92 | 100 | 67 | 0 |

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)

**Table 1.1 Summary of the incidence and severity of noteworthy microscopic observations in the Terminal females**

| **Tissue**/Observation | | | | |
|---|---|---|---|---|
| Dose Level (mg/kg) | | 0 | 120 | 600 |
| Number examined | | 12 | 2 | 6 |
| **Ovary** | | | | |
| Atrophy | **Total** | **0** | **0** | **4** |
| | Minimal | 0 | 0 | 1 |
| | Mild | 0 | 0 | 3 |
| Pigment deposit, blue/black | **Total** | **0** | **0** | **1** |
| | Mild | 0 | 0 | 1 |
| **Uterine cervix+body+horn** | | | | |
| Atrophy | **Total** | **0** | **0** | **4** |
| | Minimal | 0 | 0 | 2 |
| | Mild | 0 | 0 | 2 |
| **Vagina** | | | | |
| Atrophy | **Total** | **0** | **0** | **2** |
| | Minimal | 0 | 0 | 1 |
| | Mild | 0 | 0 | 1 |
| **Thymus** | | | | |
| Atrophy, lymphoid | **Total** | **0** | **0** | **2** |
| | Mild | 0 | 0 | 1 |
| | Moderate | 0 | 0 | 1 |
| **Lymph node, mesenteric** | | | | |
| Accumulation, pigmented | **Total** | **0** | **0** | **4** |
| macrophage | Minimal | 0 | 0 | 1 |
| | Mild | 0 | 0 | 1 |
| | Moderate | 0 | 0 | 2 |
| **Liver** | | | | |
| Vacuolation, hepatocellular | **Total** | **0** | **2** | **1** |
| | Severe | 0 | 2 | 1 |
| Necrosis, hepatocellular | **Total** | **0** | **2** | **0** |
| | Minimal | 0 | 1 | 0 |
| | Mild | 0 | 1 | 0 |
| Cell Infiltrate, | **Total** | **0** | **0** | **1** |
| mixed cellular | Minimal | 0 | 0 | 1 |

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.

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