Committee for Risk Assessment
RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

Tellurium Dioxide

EC Number: 231-193-1
CAS Number: 7446-07-3

CLH-O-0000006811-75-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted
11 June 2020

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

tellurium dioxide

EC Number: **231-193-1**

CAS Number: **7446-07-3**

Index Number: **052-RST-VW-Y**

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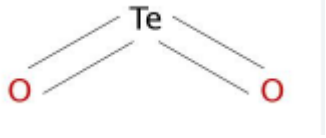
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Tellurium dioxide
Other names (usual name, trade name, abbreviation)	(oxo-λ^4-tellanyl)one
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	231-193-1
EC name (if available and appropriate)	Tellurium dioxide
CAS number (if available)	7446-07-3
Other identity code (if available)	-
Molecular formula	TeO_2
Structural formula	
SMILES notation (if available)	[O=[Te]=O]
Molecular weight or molecular weight range	159.598
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

Tellurium dioxide can exist in different crystalline structures. Under normal conditions a yellow orthorhombic (tellurite) and a colourless tetragonal form (paratellurite or alpha-TeO_2) can exist (Champarnaud-Mesjard et al., 2000; Thomas, 1988; Wells, 1995). Also amorphous forms (Dewan et al., 2008) as well as nano-tellurium dioxide are known (Arab et al., 2017). The registration dossier does not specify the crystalline structure of the substance covered by the dossier. Crystalline structures of the test items used in the different toxicological studies were also not provided. Based on the information on granulometry, which states that the median particle size of the submission substance is about 18 µm, it can reasonably be assumed that nano tellurium dioxide is not covered by the registration dossier. For some studies confidential details on the colour of the test material give an indication on the crystalline structure of the test material. According to the registrant, only one crystalline form of TeO_2 is marketed and this form has also been used in the studies. Considering this, and in the absence of any knowledge on possible differences regarding toxicological properties of the different crystalline structures of tellurium dioxide, it is assumed that the effects observed in the toxicological studies are representative for tellurium dioxide.

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Composition name	Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Tellurium dioxide – pure grade –	Tellurium dioxide (CAS No 7446-07-3)	Confidential	not applicable	**Acute Tox. 4** (H332: Harmful if inhaled) **Skin Sens. 1B** (H317: May cause an allergic skin reaction.) **Repr. 1B** (H360D: May damage fertility or the unborn child.) **Aquatic Chronic 2** (H411: Toxic to aquatic life with long lasting effects.)

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Composition name	Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Confidential					

Note: ECHA dissemination database was accessed on 09.04.2018.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not applicable					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	Not applicable										
Dossier submitters proposal	052-RST-VW-Y	tellurium dioxide	231-193-1	7446-07-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	052-RST-VW-Y	tellurium dioxide	231-193-1	7446-07-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD	-	-	-

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	data inconclusive	Yes
Carcinogenicity	data lacking	No
Reproductive toxicity	harmonised classification proposed	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling available for tellurium dioxide. The substance has not been included in former activities on harmonised classification.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

Tellurium dioxide has CMR properties (reproductive toxicity). Harmonised classification and labelling for CMR and respiratory sensitisation is a community-wide action under article 36 of the CLP regulation.

RAC general comment

The CLH dossier states that tellurium dioxide can exist in different crystalline structures. Under normal conditions, a yellow orthorhombic (tellurite) and a colourless tetragonal form (paratellurite or alpha-TeO2) can exist (Champarnaud-Mesjard *et al.*, 2000; Thomas, 1988; Wells, 1995). In addition, amorphous forms (Dewan *et al.*, 2008) as well as nano-tellurium dioxide are known (Arab *et al.*, 2017). The REACH registration dossier does not specify the crystalline structure of the substance covered by the dossier. Crystalline structures of the test items used in the different toxicological studies were not provided either. Based on granulometry information (median particle size of about 18 µm), the dossier submitter (DS) concluded that nano tellurium dioxide is not covered by the data building the basis of the CLH dossier. As there is no information on possible toxicological differences between the different crystalline forms of tellurium dioxide, RAC, in line with the DS, assumes that the effects observed in the available toxicological studies are representative for tellurium dioxide, irrespective of the crystalline structure.

Toxicokinetic information

The DS presented the data of eight studies and reviews investigating the toxicokinetics of tellurium and tellurium dioxide. These data include information on absorption, distribution, metabolism and elimination in animals and humans, as well as an *in vitro* study on the inhibiting effect of tellurium on squalene epoxidase. In addition, the solubility of tellurium and tellurium dioxide in artificial alveolar and gastrointestinal fluid has been investigated. In summary, there is no guideline toxicokinetic study available, and some of the information is limited but the following information can be extracted from the available studies.

Absorption of tellurium after oral exposure is low, up to 25% in humans (no clear differentiation between the different tellurium compounds, studies have been performed with elemental tellurium but also with tetra- and hexavalent tellurium salts). In rats and rabbits oral absorption was in the range of 10 – 40%. Tellurium can also enter the organism via the lungs (MAK, 2006). No information on dermal uptake was identified.

Tellurium is reduced to telluride after its uptake into the body, which is then stepwise methylated to mono- di- or trimethylated tellurium. These methylated forms are then excreted via urine, faeces or air. Dimethylated tellurium is the compound responsible for the typical garlic odour after intake of tellurium or tellurium dioxide. As tellurium dioxide or its reaction product with water, tellurous acid with the corresponding tellurites, is stepwise reduced in the body to telluride (Te^{2-}), the typical form of reduced tellurium in the body, it can be concluded that tellurium and tellurium dioxide are metabolised in an equivalent manner and resulting in identical metabolites. This is the basis for the read-across as can be seen in the section below.

Tellurium is eliminated as dimethyl telluride in urine, sweat and expired air, but trimethyl telluride is the predominant form in urine. Biphasic elimination was observed in rats after i.p. administration of radioactive substance. Most of orally administered tellurium was unabsorbed and appeared in the faeces. Excretion in man was about 83% via the urine, 15,6% via the faeces and 1,6% in exhaled air. In rats excretion is mainly via faeces (about 70%).

Read-across

The DS proposed a read-across with the source substance being metallic tellurium (CAS: 13494-80-9), and tellurium dioxide (CAS: 7446-07-3) as the target substance.

A read-across for the human health endpoints genotoxicity, carcinogenicity and reproductive toxicity was proposed based on the fact that the source and target substance are metabolised by the same route and because the source and target substance have very similar physico-chemical properties. On this basis, the DS hypothesised that human health toxicity, especially genotoxicity, carcinogenicity and reproductive toxicity, of source and target substance will be similar.

The DS identified Scenario 1 of the read-across assessment framework (RAAF) (ECHA, 2017a) as the most adequate scenario to perform the read-across, as the source and target substances are transformed to common compounds.

Tellurium dioxide is the oxidised form of the source substance, the metalloid tellurium. Tellurium dioxide is transformed to tellurite in the body, which is then further reduced to telluride (Te^{2-}). When tellurium enters the body it is also reduced to telluride (Te^{2-}) which is then stepwise methylated.

Ogra (2009) proposed a metabolic pathway of tellurium compounds, which was slightly adapted by the DS:

Tellurite ($(TeO_3)^{2-}$) => telluride (Te^{2-}) ➔ CH_3TeH ➔ $(CH_3)_2Te$ ➔ $(CH_3)_3Te^+$

=> reduction

➔ methylation

Since tellurium and tellurium dioxide are metabolised in a comparable way resulting in identical metabolites it is assumed that tellurium dioxide is a suitable read-across substance for tellurium.

Physico-chemical properties of both substances are very similar and both compounds are considered to have a rather low water solubility, which is also the case for tellurous acid (H_2TeO_3), the reaction product of tellurium dioxide with water. In contrast, other tellurium compounds like tellurates (TeO_4^{2-}) and tellurites (TeO_3^{2-}) have a higher water solubility.

Source and target substance have also been compared using the OECD QSAR Toolbox, and a data matrix containing information on physico-chemical as well as toxicological properties is included in the CLH dossier. The DS concluded that relevant, but limited, information was obtained by the application of the QSAR Toolbox. The results are supportive of the similarities between target and source substance.

The known toxicological properties of both substances further point towards a high degree of

concordance. Both substances have low acute toxicity, are neither skin nor eye irritant, but both give positive results in the local lymph node assay. Also the available genotoxicity and reproductive toxicity studies presented in the CLH dossier further support the similarity of source and target substance.

Read-across is performed for genotoxicity and reproductive toxicity, including effects on /via lactation and these endpoints are assessed in the CLH dossier. Carcinogenicity is not covered in the CLH dossier, as no carcinogenicity study is available, neither for tellurium nor for tellurium dioxide. Also repeated dose toxicity is not covered in the dossier, as only a 28-day and a 90-day study with tellurium dioxide are available for this endpoint.

RAC supports the analysis carried out by the DS and the applied read across.

5 IDENTIFIED USES

Tellurium dioxide is used in the manufacture of basic metals, including alloys and the manufacture of other non-metallic mineral products, e.g. plasters, cement (ECHA Dissemination, 2018). Further uses are in rubber production, and glass and ceramic industry as colouring agent (Duckett and Ellem, 1971)

Tellurium dioxide is increasingly used in optical refraction applications, for example fibre optics and complimentary products. It is an integral part of acousto-optic products and is even used for high speed or high resolution devices that need to handle high laser powers. I.e. it is used in the manufacture of re-writable optical discs, including DVDs and CDs and in acousto-optic modulators, deflectors, switches and spectrum analysers (HCN, 2002; Jha et al., 2012; Ogra et al., 2008; Voloshinov et al., 2001).

6 DATA SOURCES

Starting point for data searches for this report have been recent reviews and monographs with toxicological risk assessments on tellurium and tellurium compounds. Most relevant reviews used are Greim (2006) and HCN (2002; 2014).

Furthermore, REACH registration dossiers for tellurium (last modified: 22 November 2017) and tellurium dioxide (last modified: 15 January 2018) available from ECHA's disseminated database (ECHA Dissemination, 2018) have been analysed for study references, which then have been considered as data sources for this CLH report. In the tables with the study summaries the numbers of endpoint study records as well as the reliability evaluations as provided in the registration dossier for tellurium dioxide are provided.

Calculation of doses, if not provided in the specific references, have been performed according to and using the default values provided in the ECHA 'Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health' (ECHA, 2012).

Furthermore, ECHA guidance documents on the application of CLP criteria and on the preparation of dossiers for harmonised classification and labelling were used to compile this report (ECHA, 2014; 2017a).

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov
- TOXNET, ChemIDplus , IPCS , eChemPortal
- Medline, SciSearch, Biosis, PQscitech, Chemical Abstracts (HCA), Embase (at host STN International)

All data sources used in this report are listed in section 14 or Annex I (references).

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid, powder	(ECHA Dissemination, 2018)	measured at 20°C and 101.3 kPa;
Melting/freezing point	733°C	(Haynes, 2010)	at 101.3 kPa
Boiling point	1 245°C	(Haynes, 2010)	at 101.3 kPa
Relative density	5.9 g/cm³	(Haynes, 2010)	at 20°C and 101.3 kPa
Vapour pressure	0 Pa	(ECHA Dissemination, 2018)	estimated, a relevant vapour pressure is not assumed due to a high melting point
Surface tension	no data	(ECHA Dissemination, 2018)	expert judgement: surface activity is not expected or cannot be predicted based on the structure of the test item
Water solubility	30.72 mg/L	(ECHA Dissemination, 2018)	measured at 21.5°C and pH 8
Partition coefficient n-octanol/water	no data	(ECHA Dissemination, 2018)	study technically not feasible, test item is inorganic
Flash point	no data	(ECHA Dissemination, 2018)	study technically not feasible, test item is inorganic
Flammability	non flammable	(ECHA Dissemination, 2018)	measured
Explosive properties	none of the chemical groups in the molecule is associated with explosive properties	(ECHA Dissemination, 2018)	expert judgement
Self-ignition temperature	< 400°C; no self-ignition temperature observed up to maximum temperature	(ECHA Dissemination, 2018)	measured at 101.3 kPa
Oxidising properties	no oxidising properties	(ECHA Dissemination, 2018)	measured
Granulometry	particle size distribution of 2.84 µm, 17.74 µm, and 39.33 µm for particle sizes L10, L50, and L90	(ECHA Dissemination, 2018)	measured
Stability in organic solvents and identity of relevant degradation products	no data	(ECHA Dissemination, 2018)	study technically not feasible, test item is inorganic
Dissociation constant	no data	(ECHA Dissemination, 2018)	study technically not feasible, test item has no ionic structure
Viscosity	no data	(ECHA	study technically not feasible,

Property	Value	Reference	Comment (e.g. measured or estimated)
		Dissemination, 2018)	test item is solid

8 EVALUATION OF PHYSICAL HAZARDS

Evaluation not performed for this substance.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Measurement of the distribution of Tellurium-127m between maternal, fetal and neonatal tissues of the rat after i.v. application to dams	Labelled tellurium freely permeated the placental barrier and the maternal and fetal blood-brain barrier; relative distribution 4 h after administration: maternal tissues: kidney > liver > blood > muscle > CNS tissues > cerebrospinal fluid; fetal tissues: blood > liver > kidney > whole brain; radioactivity bound to plasma proteins and was still detectable 1 week after application	Radioactive substance: tellurous acid	(Agnew et al., 1968)
	Elimination after i.p. administration of radioactive substance in rats: biphasic, about 50% was lost within a short period ($t_{1/2}$ = 0.81 d) followed by a slower period ($t_{1/2}$ = 12.9 d); most of the orally administered tellurium was unabsorbed and appeared in the faeces, but 10-15% was absorbed; after oral administration of tellurium dioxide for 13 days to rats at level of 120 and 300 ppm in diet highest concentration were found in heart, lower and appr. similar levels in kidney, spleen, lung and bone, detectable concentrations in brain, liver and muscle; after oral ingestion of tellurium dioxide in humans the garlic odour occurred about one hour after the ingestion and persisted for one day or longer, depending on the dose	Radioactive substance: tellurous acid	(Taylor, 1996)
Investigation on tellurium induced toxicity in pups exposed via milk from dams which ingested tellurium containing diet	Tellurium is absorbed from diet and transferred to milk; exposure of pups was obvious by typical signs of tellurium toxicity and the typical garlic odour; but no analytical verification of		(Jackson et al., 1989)

Method	Results	Remarks	Reference
	tellurium in the breast milk		
Secondary source, method not provided	Tellurium is easily absorbed into the body, remains there a long time, tellurium is metabolised to dimethyl telluride, which is responsible for the garlic odour of the breath after tellurium uptake; after repeated injections of elemental tellurium black deposits in the cytoplasm of renal and neuronal cells become detectable. About 63-84% of ingested elemental tellurium is excreted by rats per day whereas the rest is retained.		(Duckett, 1970)
Review	Elemental tellurium is slowly metabolised. It is eliminated as dimethyl telluride in urine, sweat, and expired air. The average daily intake for man is not known, it is estimated to be about 0.6 mg. Oral absorption is estimated to be ca. 25%, a half-life time of 3 weeks is assumed. Excretion in man was about 83% via urine, 15.6% via the faeces, and 1.6% in exhaled air. In rats excretion is mainly via faeces (about 70%). In animals tellurium is widely distributed through the body (rat, oral single application: blood, kidneys > spleen, liver, lungs > heart, adrenal glands > muscles, brain)	Secondary source, method not described	(HCN, 2002)
In vitro studies investigating the inhibition of squalene epoxidase	Inhibition of squalene epoxidase *in vitro* was also induced by micromolar concentrations of tellurite ($(TeO_3)^{2-}$) indicating that this is the active metabolite *in vivo*.		(Wagner et al., 1995)
Review	Proposed metabolic pathway for tellurium compounds: tellurate ($(TeO_4)^{2-}$), reduction to tellurite ($(TeO_3)^{2-}$), reduction to telluride (Te^{2-}), stepwise methylation to mono-, di-, and trimethyl telluride; indicating that tellur dioxide and tellurium (in the body reduced to telluride) are ending in the same metabolism pathway; accumulation in red blood cells as dimethylated Te species which bind to hemoglobin	Review	(Ogra, 2009)
Summary of existing data *In vitro* studies on solubility in artificial body fluids	Oral absorption in rats and rabbits in the range of 10-40% of the applied dose (tellurium compound provided to rats and rabbits not indicated); inorganic		(ECHA Dissemination, 2018)

Method	Results	Remarks	Reference
	tellurium is first reduced to telluride (Te^{2-}) and thereafter methylated Solubility of tellurium dioxide in artificial alveolar and gastrointestinal fluid about three fold higher than the solubility of tellurium indicating a higher bioavailability of tellurium dioxide		

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

There is no information for tellurium dioxide from guideline toxicokinetic studies available. Limited information on the distribution of tellurous acid (H_2TeO_3), the reaction product of tellurium dioxide and water, is available from rats after intravenous injection. The registration dossier provides information on the solubility of tellurium dioxide in artificial alveolar and gastrointestinal fluid. According to Ogra (2009) tellurium dioxide or its reaction product with water, tellurous acid with the corresponding tellurites, is stepwise reduced in the body to telluride (Te^{2-}), the typical form of reduced tellurium in the body. Telluride is then methylated to mono-, di- or trimethylated tellurium, which are excreted via urine, faeces of air. Dimethylated tellurium is the compound responsible for the typical garlic odour after intake of tellurium or tellurium dioxide. Due to the fact that tellurium and tellurium dioxide are metabolised in a comparable way resulting in identical metabolites it is assumed that tellurium is a suitable read-across substance for tellurium dioxide (see section 9.2: Read-across). Therefore, experimental data for both substances, tellurium dioxide and tellurium, are reported. Information on toxicokinetics as provided in some review articles is limited in a way that most often it does not distinguish between the different tellurium compounds. However, this is not regarded as a serious drawback with respect to the overall information on toxicokinetic behaviour of tellurium and/or tellurium dioxide as the metabolic pathways are similar.

Absorption:

Absorption of tellurium (no clear differentiation between the different tellurium compounds, studies have been performed with elemental tellurium but also with tetra- and hexavalent tellurium salts) after oral exposure is low, up to 25% in humans. In rats and rabbits oral absorption was in the range of 10-40%. It can also enter the organism via the lungs (Greim, 2006). No information on dermal uptake was identified.

Distribution:

Intravenous application of tellurous acid to rat dams revealed that it freely permeated the placental barrier, the maternal and foetal blood-brain barrier. The radioactive substance bound to plasma proteins and was still detectable one week after application. Tellurium accumulated in red blood cells, probably by binding of dimethyl telluride to haemoglobin.

There is evidence that the read-across substance tellurium is transferred to milk by detection of the typical garlic odour generated by the tellurium metabolite dimethyl telluride in pups. No studies with analytical detection of tellurium or tellurium dioxide in breast milk are available.

Metabolism:

The following metabolic pathway has been proposed for tellurium compounds: tellurate ($(TeO_4)^{2-}$) is stepwise reduced via tellurite ($(TeO_3)^{2-}$) to telluride (Te^{2-}), which is then stepwise methylated to mono-, di-, and trimethyl telluride. Tellurite ($(TeO_3)^{2-}$) is typically generated in aqueous solutions of tellurium dioxide. Telluride (Te^{2-}) is the reduced form of metallic tellurium found in the body.

Excretion:

Tellurium is eliminated as dimethyl telluride in urine, sweat, and expired air; in urine the predominant metabolite was trimethyl telluride. Biphasic elimination was observed in rats after i.p. administration of radioactive substance: about 50% was excreted within a short period ($t_{1/2}$ = 0.81 d) followed by a slower period ($t_{1/2}$ = 12.9 d). Most of orally administered tellurium was unabsorbed and appeared in the faeces. Excretion in man was about 83% via the urine, 15.6% via the faeces, and 1.6% in exhaled air. In rats excretion is mainly via faeces (about 70%).

9.2 Read-across

9.2.1 Outline: primary considerations

The source substance is metallic tellurium (CAS no. 13494-80-9) and the target substance tellurium dioxide (CAS no.7446-07-3).

A read-across for the human health endpoints genotoxicity, carcinogenicity and reproductive toxicity is intended based on the fact that the source and target substance are metabolised by the same route. Additionally, both substances have very similar physico-chemical properties. This forms the basis for the hypothesis that human health toxicity, especially genotoxicity, carcinogenicity and reproductive toxicity of the source and target substance will be similar.

Scenario 1 has been identified as the most adequate scenario to perform the read-across, which is presented in the Read-across assessment framework (ECHA, 2017b), because the source and target substances are transformed to common compounds. Due to the metabolism to common compounds it is assumed that the results observed in a study conducted with the source substance predicts the properties that would be observed in a study with the target substance if it were to be conducted.

9.2.2 Hypothesis for the analogue approach

The source substance tellurium is a metalloid, while tellurium dioxide is the oxidised form of tellurium. Tellurium dioxide or its reaction product with water, tellurous acid and the corresponding tellurites ($(TeO_3)^{2-}$), are stepwise reduced in the body to telluride (Te^{2-}), the typical form of reduced tellurium in the body. Telluride is then methylated to mono-, di- or trimethylated tellurium, which are excreted via urine, faeces or air (Ogra, 2009).

Proposed metabolic pathwas of tellurium compounds adapted from Ogra (2009):

Tellurite ($(TeO_3)^{2-}$) --- > telluride (Te^{2-}) → CH_3TeH → $(CH_3)_2Te$ → $(CH_3)_3Te^+$

--- > reduction

→ methylation

Dimethylated tellurium is the compound responsible for the typical garlic odour after intake of tellurium or tellurium dioxide (Duckett, 1970). Due to the fact that both compounds are metabolised in a comparable way resulting in identical metabolites it is assumed that tellurium is a suitable read-across substance for tellurium dioxide.

9.2.3 Read-across: selected endpoints

Read-across is performed for the endpoints genotoxicity and reproductive toxicity including effects on/or via lactation, which are within the scope of the proposal for harmonised classification and labelling. No read-across is performed for the endpoint carcinogenicity due to the fact that neither carcinogenicity studies performed with tellurium nor with tellurium dioxide could be identified.

Data available for the source substance are used to contribute to the overall database available for the target substance.

Specifically, these are the following studies:

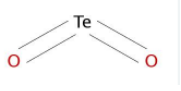
- NN (2012) reported from ECHA Dissemination (2018): Bacterial Reverse Mutation Assay performed with tellurium
- Johnson et al. (1988): Data on developmental toxicity of tellurium in rats and rabbits
- Agnew and Curry (1972); Agnew et al. (1968): Data on developmental toxicity of tellurium in rats
- Garro and Pentschew (1964): Data on developmental toxicity of tellurium in rats
- Duckett (1970), Duckett (1971), Duckett et al. (1971): Data on developmental toxicity of tellurium in rats
- Harry et al. (1989): Data on tellurium induced neuropathy in rats
- Wagner et al. (1995): Data on tellurium induced neuropathy in rats
- Jackson et al. (1989): Data on effects of tellurium administered via lactation in rats

9.2.4 Details on source substance in comparison with target substance

9.2.4.1 Identity and characterisation of the source and target substance

An overview of the identity and characterisation as provided in the registration dossier (ECHA Dissemination, 2018) of the source and target chemical is provided in Table 9.

Table 9: Identity and characterisation of the source and target substance

	Source Substance	Target Substance
Chemical name	Tellurium	Tellurium dioxide
CAS no.	13494-80-9	7446-07-3
EC no.	236-813-4	231-193-1
SMILES	[TeH2]	O=[Te]=O
Molecular formula	Te	TeO_2
Structure	Te	
MW [g/mol]	127.6	159.598
Self-Classification according to Regulation (EC) No 1272/2008[1]	**Acute Tox. 4** (H332: Harmful if inhaled) **Skin Sens. 1B** (H317: May cause an allergic skin reaction.)	**Acute Tox. 4** (H332: Harmful if inhaled) **Skin Sens. 1B** (H317: May cause an allergic skin reaction.)

[1] ECHA C&L Inventory (2017)

Information on Chemicals - Classification & Labelling Inventory

European Chemicals Agency. Online: http://echa.europa.eu/information-on-chemicals/cl-inventory, Disclaimer: http://echa.europa.eu/web/guest/legal-notice , accessed 20 March 2018

	Source Substance	Target Substance
	Repr. 1B (H360: May damage fertility or the unborn child.) **Aquatic Chronic 4** (H413: May cause long lasting harmful effects to aquatic life.)	**Repr. 1B** (H360D: May damage fertility or the unborn child.) **Aquatic Chronic 2** (H411: Toxic to aquatic life with long lasting effects.)
PBT assessment	Not performed as the substance is inorganic	Not performed as the substance is inorganic

9.2.4.2 Purity / Impurities

As far as information on the substance purity was available, read-across was performed from studies with substances of a high degree of purity. However, information on purity was not available for all studies.

9.2.4.3 Reliability and adequacy of the source studies

Both, reliable and less reliable studies were used. Some of the studies performed with the source substance were performed to investigate principle aspects of tellurium toxicity or to investigate mechanistic aspects. Therefore, they did not follow actual guidelines, or used only one dose group or only a reduced number of animals. Even for some of them the documentation is not sufficient. However, all these information contribute to the overall picture on tellurium toxicity, so that also studies with a lower reliability were considered in labelling weight-of-evidence approach.

9.2.5 Analogue approach justification

9.2.5.1 Read-across justification based on *in silico* data

In the table below **Table 10** results from QSAR Profiling of the target and the source chemicals performed with the OECD QSAR Toolbox (OECD, 2018) are shown.

Table 10: OECD QSAR Toolbox profiling

Chemical name	**Tellurium**	**Tellurium dioxide**
CAS no.	13494-80-9	7446-07-3
EC no.	380-616-2	380-250-6
Structural consistency		
US-EPA New Chemical Categories	Not categorized	Not categorized
OECD HPV Chemical Categories	Not categorized	Not categorized
Chemical elements	Group 16 - Metalloids Te,Po	Group 16 - Metalloids Te,Po
Groups of elements	Metalloids	Metalloids

Mechanistic consistency		
DNA binding by OASIS	No alert found	No alert found
DNA binding by OECD	No alert found	No alert found
Carcinogenicity (genotox and nongenotox) alerts by ISS	No alert found	No alert found
DNA alerts for AMES by OASIS	No alert found	No alert found
DNA alerts for CA and MT by OASIS	No alert found	No alert found
In vitro mutagenicity (Ames test) alerts by ISS	No alert found	No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	No alert found	No alert found
Protein binding by OASIS	No alert found	No alert found
Protein binding by OECD	No alert found	No alert found
Toxic hazard classification by Cramer (with extensions)	High (Class III)	High (Class III)
Retinoic Acid Receptor Binding	Not possible to classify according to these rules	Not possible to classify according to these rules
rtER Expert System - USEPA	No alert found	No alert found
Estrogen receptor binding	Non binder, non cyclic structure	Non binder, non cyclic structure
Acute aquatic toxicity classification by Verhaar (Modified)	Class 5 (not possible to classify according to these rules)	Class 5 (not possible to classify according to these rules)
Acute aquatic toxicity MOA by OASIS	Reactive unspecified	Reactive unspecified
Consistent bioavailability		
Lipinski Rule Oasis	Bioavailable	Bioavailable

Note: profilers were selected based on relevant ECHA guidance documents (Read-Across Assessment Framework, 2017; ECHA Illustrative Examples with the OECD QSAR Toolbox Workflow parts 1 to 2c) and supplemented based on personal experience. Please regard that similarity indices of the OECD QSAR Toolbox (e.g. Tanimoto and others as mentioned in ECHA's Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.6 Guidance on QSARs and grouping of chemicals) were not applied since their use is generally discouraged (see e.g. discussions in the OECD QSAR Toolbox Forum at https://community.oecd.org/thread/14418?tstart=0 and ECHA's Practical Guide "How to use alternatives to animal testing to fulfil your information requirements for REACH registration"

The high structural similarity between source and target is mirrored by the *in silico* analysis on structural consistency. Both substances are metalloids and belong to Cramer Class III, *i.e.* substances with a high level of concern with regard to toxic properties.

However, no conclusions can be drawn with regard to most other profilers with special emphasis on possible genotoxic, hormonal or environmental effects, as the underlying rules do not apply to inorganic substances.

With regard to bioavailability profiling, according to Lipinski Rules, both source and target are classified as bioavailable.

In conclusion, the limited relevant information provided by the *in-silico* analysis as described in **Table 10** above is consistent with the structural similarity of the source and target substance. But no conclusions on possible genotoxic, hormonal or environmental effects could be drawn, as the underlying rules do not apply to inorganic substances.

9.2.5.2 Read-across justification based on substance specific data

For a compilation of available physico-chemical and human health data for the source and target substance, please see section 9.2.6 below.

Physico-chemical properties of both substances are very similar. Tellurium and tellurium dioxide are solids with a very high boiling point. Due to this high boiling point the vapour pressure was estimated to be equal to zero. Both compounds are only slightly soluble in water . Tellurous acid, the reaction product of tellurium dioxide with water, is also only barely soluble in water. This makes the difference to other tellurium compounds like tellurates and tellurites, which are soluble in water.

The toxicological properties of the source substance tellurium and the target substance tellurium dioxide also point to a high degree of concordance. Both substances did not reveal lethality after single oral application up to 5000 mg/kg. Also no lethality was observed after inhalation exposure up to 2.4 g/m^3. Both substance are neither skin nor eye irritant, but were tested positive in the Local Lymph Node Assay for skin sensitising properties.

Available *in vitro* assays on genotoxicity revealed negative results for both substances. Also the numerous studies on developmental effects after tellurium or tellurium dioxide exposure point to similar toxicity of both substances with the induction of hydrocephali in *in utero* exposed pups being a typical malformation which can be observed in all studies.

No comparison for repeated dose toxicity is possible as only studies with tellurium dioxide are available for this endpoint. Also reproductive effects on fertility are only available for tellurium dioxide. However, based on the high degree of concordance for the other endpoints and the fact that identical metabolites are generated under physiological conditions it can reasonably be assumed that both substances would also show comparable results for these endpoints.

In summary, a very high degree of concordance for physico-chemical and human health effects can be ascertained.

9.2.6 Data matrices

The physicochemical profiles of the target and source substances are highly similar as outlined in the data matrix (Table 11). However, some physico chemical properties (*e.g.* surface tension, viscosity, dissociation constant) could not be determined due to the fact that the substances are inorganic.

Table 11: Data matrix on comparative data for target and source substances; data were taken from REACH registration dossiers (ECHA Dissemination, 2018) if not indicated otherwise.

	Source substance	**Target substance**
Chemical name	Tellurium	Tellurium dioxide
CAS no.	13494-80-9	7446-07-3
EC no.	236-813-4	231-193-1
Physico-chemical properties		

	Source substance	Target substance
Chemical name	Tellurium	Tellurium dioxide
Physical state	Solid, powder	Solid, powder
Melting Point [°C]	450°C	733°C
Boiling Pont [°C]	988°C at 1013 hPa	1 245°C at 1013 hPa
Relative Density	6.232 g/cm³ at 20°C	5.9 g/cm³ at 20°C
Vapour pressure [Pa]	0 Pa, estimated	0 Pa, estimated
Partition coefficient (log Pow)	No data	No data
Water solubility at 20°C	1.762 mg/L	30.72 mg/L (pH 8)
Surface tension [mN/m]	No data	No data
Flash point [°C]	No data	No data
Flammability	Non-flammable	Non-flammable
Explosiveness	Non-explosive, estimated	Non-explosive, estimated
Oxidizing properties	no oxidising properties	No oxidising properties
Stability in organic solvents and identity of relevant degradation products	No data	No data
Dissociation constant	No data	No data
Viscosity	No data	No data
Human Health		
Acute toxicity	LD_{50} oral rat or mice: > 5000 mg/kg LC_{50} inhal. rat: > 2.42 g/m³ LD_{50} dermal rat: no data available	LD_{50} oral rat: > 5000 mg/kg LC_{50} inhal. rat: > 2.42 g/m³ LD_{50} dermal rat: no data available
Skin Irritation/Corrosion	Not irritating	Not irritating
Eye Irritation	Not irritating	Not irritating
Skin Sensitisation	Skin sensitising (positive reaction in Local Lymph Node Assay; no clear dose response; EC3 values 3.2, 3.2 and 3.8 at treatment concentrations of 100, 50 and 25% (w/v), respectively)	Skin sensitising (positive reaction in Local Lymph Node Assay; no clear dose response; EC3 values 3.7, 2.0 and 3.9 at treatment concentrations of 100, 50 and 25% (w/v), respectively)

	Source substance	Target substance
Chemical name	Tellurium	Tellurium dioxide
Genotoxicity	Bacterial Reverse Mutation Assay: negative (strains TA 1535, TA 1537, TA98 and TA100 of S. typhimurium and E. coli WP2 uvrA were exposed to Tellurium, (powder 99.95 % a.i.), at concentrations up to 5000 µg/plate in the presence and absence of mammalian metabolic activation, (S9 mix; phenobarbital/β-naphthoflavone induced rat liver); initial test: plate incorporation method; confirmatory assays: pre-incubation method)	Bacterial Reverse Mutation Assay: negative (strains TA 1535, TA 1537, TA98 and TA100 of S. typhimurium and E. coli WP2 uvrA were exposed to Tellurium dioxide, (powder 99.9 % a.i.), at concentrations up to 5000 µg/plate in the presence and absence of mammalian metabolic activation, (S9 mix; phenobarbital/β-naphthoflavone induced rat liver); initial test: plate incorporation method; confirmatory assays: pre-incubation method) *In vitro* gene mutation assay (Mouse Lymphoma Assay): negative *In vitro* cytogenicity assay (Chromosome Aberration Assay): negative

	Source substance	Target substance
Chemical name	Tellurium	Tellurium dioxide
Reproductive toxicity	Fertility: RA from tellurium dioxide Developmental toxicity: $NOAEL_{maternal\ oral/feed}$ rat: 30 ppm (1.9 mg/kg bw/d) $LOAEL_{maternal\ oral/feed}$ rat: 300 ppm (18 mg/kg bw/d); effects: inter alia reduced feed consumption and body weight gain $NOAEL_{developmental\ oral/feed}$ rat: 300 ppm (18 mg/kg bw/d) $LOAEL_{developmental\ oral/feed}$ rat: 3000 ppm (173 mg/kg bw/d); effects: skeletal and soft tissue malformations, primarily hydrocephali $NOAEL_{maternal\ oral/feed}$ rabbit: 175 ppm (ca. 7 mg/kg bw/d) $LOAEL_{maternal\ oral/feed}$ rabbit: 1750 ppm (ca. 70 mg/kg bw/d); effects: inter alia reduced feed consumption and body weight gain $NOAEL_{developmental\ oral/feed}$ rabbit: 1750 ppm (ca. 70 mg/kg bw/d) $LOAEL_{developmental\ oral/feed}$ rabbit: 5250 ppm (ca. 210 mg/kg bw/d); effects: inter alia increased incidence of foetuses or litters with variations, malformations including hydrocephalus	Fertility: OECD TG 421 screening study: $NOAEL_{reproduction}$ females: 25 mg/kg bw/d $NOAEL_{reproduction}$ males: 600 mg/kg bw/d $NOAEL_{systemic}$ females/males: 25 mg/kg bw/d Developmental toxicity: $NOAEL_{maternal\ subcutaneous}$ rat: 100 µmol/kg bw/d (ca. 16 mg/kg bw/d) $LOAEL_{maternal\ subcutaneous}$ rat: 500 µmol/kg bw/d (ca. 80 mg/kg bw/d); effects: inter alia weight loss $NOAEL_{developmental\ subcutaneous}$ rat: 10 µmol/kg bw/d (ca. 1.6 mg/kg bw/d) $LOAEL_{developmental\ subcutaneous}$ rat: 100 µmol/kg bw/d (ca. 16 mg/kg bw/d); effects: high incidence of hydrocephalus (already 100% at LOAEL) OECD TG 421 screening study: $LOAEL_{developmental}$: 25 mg/kg bw/d

Note: Data for source and target substance was extracted from the REACH registration dossier[2], accessed 15 March 2018.

[2] ECHA Dissemination (2018)

Information on Chemicals - Registered Substances

European Chemicals Agency. Online: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances, accessed October 2017

9.2.7 Conclusions per endpoint for C&L, PBT/vPvB and dose descriptor

Key data presented above substantiate similar physico-chemical profiles of the target substance tellurium dioxide and the source substance tellurium. Additionally, source and target substance are metabolically transformed to common compounds.

This similarity assumption is corroborated by the *in silico* analysis, which confirms that structural properties of the source substance and target substance are the same (see section 9.2.5.1). Data of source substance is therefore used to supplement the data on the endpoints genotoxicity and reproductive toxicity regarded in the proposal for harmonised classification and labelling.

Based on the available data provided in the data matrix of the preceding chapter, a read-across is justified for the human health endpoints genotoxicity and reproductive toxicity.

The dose descriptors in the studies were converted taking into account the different molecular weights for the source and target substance.

In conclusion, read-across for data on genotoxicity and reproductive toxicity is considered adequate to take into account all relevant aspects for the proposed harmonised classification. This conclusion is based on the justifications given above, which were substantiated by reliable data.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Evaluation not performed for this substance.

10.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

10.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

10.4 Skin corrosion/irritation

Evaluation not performed for this substance.

10.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

10.6 Respiratory sensitisation

Evaluation not performed for this substance.

10.7 Skin sensitisation

Evaluation not performed for this substance.

10.8 Germ cell mutagenicity

Table 12: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial gene mutation OECD TG 471 Deviations: no Ames Test GLP: yes RL1[#] (according to registration dossier and the authors of this document)	Tellurium dioxide (information on purity: see confidential annex)	Salmonella typhimurium TA 1535, TA1537, TA 98, TA 100 and E.coli WP2uvrA Plate incorporation-Range finding test (only TA 98 and TA 100) 10, 31.6, 100, 316, 1000, 2500, 5000 µg TeO_2/plate Plate incorporation-Initial test (all strains): 1.581, 5, 15.81, 50, 158.1, 500, 1581, 5000 µg TeO_2/plate Pre-incubation (all strains): 0.5, 1.581, 5, 15.81, 50, 158.1, 500, 1581 µg TeO_2/plate Pre-incubation – confirmation (TA 1535 without MA[###]): 0.005, 0.01581, 0.05, 0.1581, 0.5, 1.581, 5, 15.81 µg TeO_2/plate Pre-incubation – confirmation TA98, TA 100, TA 1537 without MA: 0.001581, 0.005, 0.01581, 0.05, 0.1581, 0.5, 1.581 µg TeO_2/plate Tested up to limit concentration Vehicle: 1 % (v/v) methyl cellulose solution +/- S9 mix of phenobarbital/β-naphthoflavone induced rat liver Positive controls: yes	Negative (+/- S9 mix) for all strains tested Confirmation tests were performed due to high cytotoxicity	NN, 2012[##] reported from (ECHA Dissemination, 2018)
Bacterial gene	Read-across substance tellurium (information on	Salmonella typhimurium TA 1535, TA1537, TA 98, TA	Negative (+/- S9 mix) for all strains tested	NN, 2012 reported from (ECHA

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
mutation OECD TG 471 Deviations: no Ames Test GLP: yes RL1 (according to registration dossier and the authors of this document)	purity: see confidential annex)	100 and E.coli WP2uvrA Plate incorporation-Range finding test (only TA 98 and TA 100) 10, 31.6, 100, 316, 1000, 2500, 5000 µg Te/plate Plate incorporation-Initial test (all strains): 5, 15.81, 50, 158.1, 500, 1581, 5000 µg Te/plate Pre-incubation (all strains): 1.581, 5, 15.81, 50, 158.1, 500, 1581, 5000 µg Te/plate Pre-incubation – confirmation (at least TA 1535, 1538, TA100, WP2uvrA as information on cytotoxicity was reported for these strains): 0.05, 0.1581, 0.5, 1.581, 5, 15.81, 50, 158.1 µg Te/plate Tested up to limit concentration Vehicle: 1 % (v/v) methyl cellulose solution +/- S9 mix of phenobarbital/β-naphthoflavone induced rat liver Positive controls: yes	Confirmation tests were performed due to high cytotoxicity	Dissemination, 2018)
Chromosome aberration study in mammalian cells OECD TG 473 Deviations: no GLP: yes RL1 (according to registration	Tellurium dioxide (information on purity: see confidential annex)	Chinese hamster lung fibroblasts (V79) Assay 1: 3-hr treatment <u>without</u> S9-mix, harvest 20 hours from the beginning of treatment: concentrations: 200, 100, **75, 50, 25**, 12.5, 6.25 and 3.125 µg TeO_2/mL 3-hr treatment <u>with</u> S9-mix, harvest 20 hours	Negative (+/- S9 mix)	NN, 2013 reported from (ECHA Dissemination, 2018)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
dossier and the authors of this document)		from the beginning of treatment: concentrations: 200, **100, 75, 50**, 25, 12.5, 6.25 and 3.125 µg TeO_2/mL Assay 2: 20-hr treatment <u>without</u> S9-mix, harvest 28 hours from the beginning of treatment: concentrations: 60, 40, 30, 20, 15, **10, 7.5, 5** and 2.5 µg TeO_2/mL 3-hr treatment <u>with</u> S9-mix, harvest 28 hours from the beginning of treatment: concentrations: 200, 100, **75, 50, 25, 12.5**, 6.25 and 3.125 µg/mL (concentrations marked in bold were evaluated, other concentrations were too cytotoxic) Vehicle: : 1 % (v/v) methyl cellulose solution +/- S9 mix of phenobarbital/β-naphthoflavone induced rat liver Positive controls: yes		
Gene mutation study in mammalian cells OECD TG 476 Deviations: no GLP: yes RL1 (according to	Tellurium dioxide (information on purity: see confidential annex)	Mouse lymphoma L5178Y cells Target gene: Thymidine kinase (TK) Assay 1: 3-hour treatment with metabolic activation: 100; 75; 50; 25; 20; 15; **10; 7.5; 5; 2.5; 1.25 and 0.625** µg TeO_2/mL Assay 1: 3-hour treatment without metabolic activation:	Negative (+/- S9 mix) Assay 1 with MA: statistically significant increases in the mutation frequency at 10, 7.5, 5, 2.5, 1.25 µg/mL; however GEF (global evaluation factor) only exceeded at 7.5, 5 and 2.5 µg/mL, not at 10 and 1.25 µg/mL; therefore results not regarded as relevant as no clear dose-response was observed. Assay 1 without MA: statistically significant increase in the mutation frequency only at 20 µg/mL,	NN, 2013 reported from (ECHA Dissemination, 2018)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
registration dossier and the authors of this document)		80; 70; 60; 50; 40; 30; **20; 10; 5; 2.5; 1.25 and 0.625** µg TeO_2/mL Assay 2: 3-hour treatment with metabolic activation: 20; 17.5; 15; 12.5; 10; 7.5; **5; 2.5; 1.25 and 0.625** µg TeO_2/mL Assay 2: 24-hour treatment without metabolic activation: 15; 12.5; 10; 9; 8**; 7; 6; 5; 4; 2; 1; 0.5 and 0.25** µg TeO_2/mL Test substance concentrations were selected based on cytotoxicity (concentrations marked in bold were evaluated, other concentrations were too cytotoxic) Vehicle: : 1 % (v/v) methyl cellulose solution +/- S9 mix of phenobarbital/β-naphthoflavone induced rat liver Positive controls: yes	however, GEF not exceed, therefore result not biologically relevant Assay 2 with MA: statistically significant increase in the mutation frequency only at 5 µg/mL, however, GEF not exceed, therefore result not biologically relevant. This repeat did not confirm the observations from Assay 1 with MA. Assay 2 without MA: statistically significant increase in the mutation frequency only at 8 µg/mL, however, GEF not exceed, therefore result not biologically relevant.	

[#] RL1, RL2, RL3, or RL4 refers to Klimisch Reliability Scores 1, 2, 3, or 4

[##] NN = Nomen nescio

[###] MA = metabolic activation

Table 13: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no *in vivo* data available				

Table 14: Summary table of human data relevant for germ cell mutagenicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no human data available				

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

There are only *in vitro* data available for the assessment of germ cell mutagenicity of tellurium dioxide, which are summarized in Table 12. No *in vivo* data and no human data were identified.

Gene mutation *in vitro* was assessed in a bacterial reverse mutation assay according to OECD guideline 471 and GLP. Tellurium dioxide was negative in all strains, both in the plate incorporation assay and the pre-incubation assay in the presence and absence of metabolic activation. Comparable results were obtained with the read-across substance tellurium, which also did not induce gene mutations in a reliable Ames assay, both in the presence and absence of metabolic activation.

Clearly negative results were also obtained in an *in vitro* chromosome aberration assay, both in the presence and absence of a metabolic activating system.

In a mouse lymphoma assay L5178Y cells were exposed with and without metabolic activation for 3 hours and for 24 hours without metabolic activation. Excessive cytotoxicity was observed at concentrations equal or above 20 µg/mL, so that only low concentrations could be evaluated. In Assay 1, following a 3-hour treatment with metabolic activation, statistically significant increases in the mutation frequency were observed at the four concentrations evaluated (10, 7.5, 5, 2.5, 1.25 µg/mL). However, the difference between the mutation frequency of the test item treated sample and the corresponding vehicle control value did not exceed the Global Evaluation Factor (GEF, a validity criterion recommended in the guideline to assess the biological relevance of statistical significant increases) in case of the 7.5, 5 and 2.5 µg/mL concentrations, thus they were considered as biologically non relevant increases. In case of the 10 and 1.25 µg/mL concentrations, the values were above the limit of the biological relevance (the difference was higher than the global evaluation factor) but the results did not follow a clear dose response and the increases were not reproduced in Assay 2 (repetition under identical conditions: 3-hour treatment with metabolic activation).

Also in Assay 1 with 3 hours treatment without metabolic activation and in Assay 2 with 24 hours treatment without metabolic activation statistically significant increases in the mutation frequency were observed at the highest concentrations evaluated. However, the difference between the mutation frequency of the test item treated sample and the corresponding vehicle control value did not exceed the global evaluation factor, and are therefore not considered as biologically relevant. Therefore, the results of this assay are regarded as clearly negative.

In summary, negative results were obtained in all three *in vitro* assays performed with tellurium dioxide and in the bacterial reverse mutation assay performed with the read-across substance tellurium.

10.8.2 Comparison with the CLP criteria

There are no epidemiological data to support classification of tellurium dioxide in Category 1A.

In the absence of any *in vivo* germ cell or somatic cell mutagenicity tests there is no evidence that the substance has the potential to cause germ cell mutations. Classification in Category 1B is not justified.

In the absence of any *in vivo* somatic cell genotoxicity data and with only negative results from *in vitro* assays there is no evidence that the substance has the potential to cause somatic cell mutations. Thus, classification in Category 2 is not justified.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

As outlined in section 10.8.2 only negative results were obtained in *in vitro* assays with tellurium dioxide or the read-across substance tellurium and no *in vivo* or epidemiological data are available. Therefore, none of the criteria for classification for germ cell mutagenicity is fulfilled.

Therefore no classification as a germ cell mutagen is proposed for tellurium dioxide.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The CLH dossier provides three *in vitro* studies with tellurium: a bacterial gene mutation study (OECD TG 471, GLP; Anonymous, 2012b), a chromosome aberration study in mammalian cells (OECD TG 473, GLP; Anonymous, 2013a) and a gene mutation study in mammalian cells (OECD TG 476, GLP; Anonymous, 2013b) as well as one bacterial gene mutation study (OECD TG 471, GLP; Anonymous, 2012a) with the read-across substance tellurium.

No *in vivo* studies are available.

The OECD TG 471 (Anonymous, 2012b) study with tellurium dioxide was clearly negative in all strains, both in the plate incorporation assay and the pre-incubation assay in the presence and absence of metabolic activation. In addition, tellurium gave negative results in a comparable study (OECD TG 471, Anonymous, 2012a).

Clearly negative results were also obtained in an *in vitro* chromosome aberration assay with tellurium dioxide (OCDE 473, Anonymous, 2013a).

In a mouse lymphoma assay with tellurium dioxide (OECD TG 476, GLP; Anonymous, 2013b) L5178Y cells were exposed with and without metabolic activation for 3 hours and for 24 hours without metabolic activation. Excessive cytotoxicity was seen at doses ≥ 20µg/mL, so that only low concentrations could be evaluated. After 3 hours with metabolic activation (Assay 1) statistically significant increases in the mutation frequency were observed at the four concentrations evaluated (10, 7.5, 5, 2.5, 1.25 µg/mL). However, the difference between the mutation frequency of the test item treated sample and the corresponding vehicle control value did not exceed the Global Evaluation Factor (GEF, a validity criterion recommended in the guideline to assess the biological relevance of statistical significant increases) in case of the 7.5, 5 and 2.5 µg/mL concentrations. Thus, they were considered as biologically non-relevant increases. In case of the 10 and 1.25 µg/mL concentrations, the values were above the limit of the biological relevance (the difference was higher than the GEF), but the results did not follow a clear dose response and the increases were not reproduced in Assay 2 (repetition under

identical conditions: 3 hours treatment with metabolic activation).

Overall, the DS concluded that tellurium dioxide and the read across substance tellurium were clearly negative in the available *in vitro* tests.

Comments received during public consultation

One Member State Competent Authority (MSCA), one trade organisation and one company supported no classification for germ cell mutagenicity based on the *in vitro* genotoxicity studies presented in the dossier.

Additional key elements

In a review by MAK (2006), which is also referred to in the CLH dossier, though not under the section on germ cell mutagenicity, it is concluded that tellurium compounds cause direct damage to the DNA with mutagenic effects in bacteria, and are clastogenic in mammalian cells. This is based on several *in vitro* mutagenicity studies with different tellurium compounds. The majority of these studies, including several bacterial reverse mutation assays, a chromosome aberration test in human leukocytes and a micronucleus test in human lymphocytes gave positive results. One of the positive bacterial reverse mutation studies was conducted with tellurium dioxide (Yagi & Nishioka, 1977). No studies with tellurium were located.

As the other compounds that were tested are not in focus of the present opinion, only the study on tellurium dioxide is considered relevant. The other compounds are considered to have different properties, for instance the water solubility of tellurates and tellurites is clearly higher than that of metallic tellurium and tellurium dioxide (see RAC general comment).

Yagi & Nishioka (1977) tested several metal compounds in a non-guideline *in vitro* DNA repair test for their mutagenic potential. In a previous screening test with two strains, they had tested 56 metal compounds, of which 14 gave positive results. The positive substances, among them TeO_2 as well as $Na_2H_4TeO_6$, were further tested in the so-called streak test using 4 different bacterial strains (E. coli WP2 (uvrA+, recA+), WP2uvrA (uvrA-, recA+), CM571 (uvrA+, recA-) and WP100 (uvrA-, recA-)). The applied concentration was 1 mg/mL for both tellurium compounds, TeO_2 was dissolved in diluted HCl, NaH_4Te_6 was dissolved in diluted HNO_3. The principle of the test is based on the fact that bacterial cells deficient in DNA repair capacity are more susceptible to DNA attacking agents than wild type cells. The read-out was the difference in growth inhibition (DIG) which could be either –, + or ++. Both tellurium compounds gave a positive result (+). Overall, the information presented on the test system is rather scarce and no firm conclusion can be drawn.

Assessment and comparison with the classification criteria

RAC agrees with the DS's analysis and interpretation of the *in vitro* mutagenicity studies presented in the CLH dossier. No indication for a mutagenic potential of neither tellurium dioxide nor tellurium can be derived from the presented *in vitro* studies.

However, it is noted that the available studies have some limitations. For the bacterial reverse mutation assay (OECD TG 471, Anonymous, 2012b) it is reported that cytotoxicity was observed in the two or three highest concentrations of the Initial Mutation Test, where the plate incubation technique was used. Stronger cytotoxicity (no further detail) was seen in the Confirmatory and Complementary Confirmatory Mutation Tests, where the pre-incubation test was used, leaving doubts regarding which doses cytotoxicity was actually seen. As for

tellurium, water solubility is also rather low for tellurium dioxide, but no formation on precipitates is reported, although concentrations up to 5000 µg/plate were tested.

In contrast, in the *in vitro* mammalian gene mutation test (OECD TG 476, Anonymous, 2013b), in which the same vehicle (methyl cellulose) was used, it is described that for some concentrations insolubility was detected in the final treatment medium at the end of treatment. No further details on the exact concentrations where insolubility occurred is presented. Due to the excessive cytotoxicity only rather low doses could be tested (Assay 1, with metabolic activation: ≤ 10 µg/mL, Assay 1, without metabolic activation: ≤ 20 µg/mL, Assay 2, with metabolic activation: ≤ 5 µg/mL, Assay 2, without metabolic activation: ≤ 8 µg/mL).

Also for the *in vitro* mammalian chromosome aberration test (OECD TG 473, Anonymous, 2013a) inconsistencies were observed with regard to concentrations at which cytotoxicity and precipitation occurred. While in Assay 2 without metabolic activation cytotoxicity was seen as low as 10 µg/mL, in the other assays cytotoxicity only started at 75 or 100 µg/mL. "Minimum" solubility was reported in three of the four assays at 100 and 200 µg/mL.

Also in the bacterial reverse mutation assay with tellurium (OECD TG 471, GLP; Anonymous, 2012a), no information on the formation of precipitates is presented. However, as the substance has a rather low water solubility it can be assumed that at the tested doses some precipitation may have occurred.

Regarding cytotoxicity it is stated that it was seen only in the top dose of 5000 µg/plate in the Initial Mutation Test, but at clearly lower doses in the Confirmatory and the Complementary Confirmatory Mutation Test: in the test strain E. coli WP2 uvrA at concentrations of 5000, 1581 & 500 µg/plate and in the test strains TA100, TA1535 & TA1537 at 158.1 and 50 µg/plate (it is unclear if in these strains cytotoxicity was not seen at higher doses). These results are on the one hand conflicting and, on the other hand, leave only few lower dose concentrations for the assessment of possible genotoxic potential of the test material.

Overall, there are minor limitations in the presented *in vitro* mutagenicity studies, but no indication for a mutagenic potential can be derived.

RAC noted that in a review by MAK (2006) further *in vitro* genotoxicity studies with several tellurium compounds are described. Several of these studies, including a DNA repair study in bacterial cells with the read across substance tellurium dioxide (Yagi & Nishioka, 1977), gave positive results (see section above in Additional key elements). It is, however, noted that the study did not follow generally accepted guidelines and the information presented on the test system is rather scarce.

It can be concluded that the well-conducted *in vitro* genotoxicity studies presented in the CLH dossier have some minor deficiencies with regard to solubility and cytotoxicity and reporting thereof and it is not clear whether these issues interfered with the tests ability to detect any mutagenic potential, but gave negative results. A non-guideline study by Yagi & Nishioka, 1977 gave a positive result.

On this basis and in the absence of any *in vivo* study, **no classification for germ cell mutagenicity is proposed**.

10.9 Carcinogenicity

Table 15: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Not applicable since no animal data available			

Table 16: Summary table of human data on carcinogenicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no human data available				

Table 17: Summary table of other studies relevant for carcinogenicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no data available				

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

There are no studies available which investigate the potential carcinogenic effect or chronic toxicity of tellurium dioxide. In a sub-chronic oral toxicity study in rats according to OECD TG 408 and GLP (RL1 according to registrations dossier) no evidence of potential carcinogenic effects was observed (no neoplastic lesions or other irreversible effects) (ECHA Dissemination, 2018).

Also for the read-across substance tellurium no studies investigating carcinogenic effects were identified.

Potential carcinogenic effects of tellurium compounds were investigated by Schroeder and Mitchener (1971; 1972) in rats and mice which were exposed via drinking water to the soluble tellurium compounds sodium tellurite or potassium tellurite. These studies did not indicate any carcinogenic properties of these soluble tellurium compounds. However, these studies were judged to be of no relevance for the evaluation of possible carcinogenic effects of tellurium dioxide due to the fact that a) the studies were performed with soluble tellurium compounds which possibly differ in their bioavailability and b) the shortcomings of these

investigations (*e.g.* high mortality in rats due to pneumonia, the use of only one dose, the fact that histopathological investigations were not performed for all animals, insufficient reporting (tumour types and incidences not provided)), which limit the reliability of the studies (Greim, 2006).

Table 18: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Not applicable								

10.9.2 Comparison with the CLP criteria

In the absence of relevant and reliable studies on possible carcinogenic effects in humans and experimental animals and in the absence of any indications of carcinogenic effects from a repeated dose toxicity study the criteria are not applicable and classification for tellurium as a carcinogen cannot be assessed.

10.9.3 Conclusion on classification and labelling for carcinogenicity

In the absence of relevant and reliable studies on potential carcinogenic effects of tellurium dioxide the classification for carcinogenicity cannot be assessed.

Therefore no classification as a carcinogen is proposed for tellurium dioxide.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 19: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Reproduction / Developmental Toxicity Screening Test OECD TG 421 Deviations: no GLP: yes Male/female Wistar rats 12 animals per	Tellurium dioxide (information on purity: see confidential annex) 0, 25, 120 and 600 mg TeO_2/kg bw/d,	<u>P0:</u> NOAEL systemic effects: 25 mg TeO_2 /kg bw/d for male and female rats: - mortality in females of HD# (five females found dead between days 14 and 45; one female died on day 27 due to gavage accident, one female found dead on day 13 of mating period); - effects on clinical signs (in females found dead: *i.a.* decreased activity, liquid faeces, hunched back, laboured respiration, lethargy, piloerection and red liquid from the mouth and vulva, dark faeces, but similar effects also in females at scheduled necropsy),	NN, 2013 reported from (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
sex and dose group RL1 (according to registration dossier and the authors of this document)	Exposure: Males were dosed for 28 days (14 days pre-mating and 14 days mating/post-mating). They were sacrificed afterwards. Females were exposed 14 days pre-mating, for up to 14 days of mating (1:1), throughout gestation and up to day 4 of lactation, which was the day before necropsy. Application via gavage, 7 days/week Vehicle: 1 % (v/v) methyl cellulose solution	- reduced body weight or body weight gain and food intake in males and females of MD and HD (terminal body weights in males of MD and HD about 7% and 14% lower than control, in females the day 14 body weights were about 5% and 11% below controls in the MD and HD group) - females: histopathological findings in MD (only liver) and HD (including reproductive organs as well as other organs) - males MD and HD: histopathological findings: dose-related accumulation of pigmented macrophages in the mesenteric lymph nodes NOAEL reproductive toxicity: 25 mg TeO_2/kg bw/d - Reduced mating and fertility index in HD females, 73% and 63%, respectively (100% in all other dose groups); - reduced gestation index (number of females with live born pups/ number of pregnant females x 100) in MD and HD females: 92, 100, 62, 0% in control, LD, MD, HD, respectively; - four (4/6) females from the HD group were non-pregnant, a decrease or no corpora lutea and no implantation sites were seen in these animals at necropsy; - oestrus cycle of females of the HD was characterised by dioestrus; - at MD the gestation period was prolonged; - in dead HD females: atrophy of reproductive tissues (minimal to moderate atrophy of the ovary, uterus and/or vagina in 3/5 females, moderate vacuolation of corpora lutea in the right ovary in 1/5 female, mild blue/black diffuse pigment deposits of the right ovary in 1/5 animal); in other females of HD also histopathologic changes of reproductive organs as well as on kidney, liver and thymus (histopathology only in control and HD animals); - in males no effects on reproductive function, weight and histopathology of reproductive organs or sperm parameter were observed up to the highest dose. <u>F1:</u> LOAEL: 25 mg TeO_2/kg bw/d (increased pup mortality at all dose groups) Remark: Special attention was paid to the evaluation of the stages of spermatogenesis in the male gonads and histopathology of interstitial testicular cell structure.	

[#] LD, MD, HD refer to low dose, mid dose and high dose

Table 20: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no human data available				

Table 21: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Subchronic oral toxicity study in Wistar rats According to OECD TG 408 GLP: yes RL1 (according to registration dossier and the authors of this document)	Tellurium dioxide (Purity: no information provided) 0, 10, 30, 100 mg TeO_2/kg bw/d Application via gavage	Special attention was paid to male reproductive endpoints: seminiferous tubules evaluation with respect to stage in the spermatogenic cycle and to the integrity of the various cell types within the different stages	NOAEL: 100 mg TeO_2/kg bw/d Findings for male reproductive organs: no effects, regular layering in the germinal epithelium; no differences at sperm analysis including sperm motility and concentration, and cauda weight between the control and the high dose group at the end of treatment.	NN, 2017 reported from (ECHA Dissemination, 2018)

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

There are no human studies addressing adverse effects on sexual function and fertility of tellurium or tellurium dioxide available.

Animal experimental data are available from a reliable screening study according to OECD TG 421. This study clearly revealed decreased fertility in parental animals of the mid (MD) and high dose (HD). Effects on fertility (reduced mating and fertility indices) were most pronounced at doses, which caused severe toxicity, *i.e.* in the high dose group, which induced mortality in females. Further, a reduced gestation index was observed in MD and HD females (62, 0%, respectively) and an increased gestation period (no further information provided at the ECHA dissemination site) was observed in the MD. Changes in these indices can be due to effects on male or female reproduction, no distinction can be made only on basis of these indices. However, investigations on male reproductive organs did not point to any adverse effects. On the other side, there is additional information available, which indicates that female reproduction might be influenced by tellurium dioxide exposure.

Four (4/6) females from the HD group were non-pregnant, a decrease or no corpora lutea and no implantation sites were seen in these animals at necropsy pointing to serious effects on female reproduction. Additionally, histopathology *inter alia* revealed atrophy of female reproductive tissues in the HD group, both in animals found dead and at scheduled termination. According to the information from the ECHA

dissemination site '*There was a consistent relationship to dose in the severity and incidence of these test item-related microscopic effects*.' However, detailed histopathologic results were not documented in the registration dossier. In the executive summary of the registration dossier, it is stated that '*The reproductive organ effects in females are not considered to be secondary effects of systemic toxicity.*' The authors of this documentation share this opinion, as atrophy of reproductive organs is no common finding in animals, which suffer from severe toxicity up to lethality.

The absence of effects especially on reproductive organs in male animals in the reproductive screening study is in accordance with the findings of a sub-chronic toxicity study in rats, which also did not observe any toxicity on male reproductive organs. In the sub-chronic study also no effects on female reproductive organs were described. This is not in disagreement to the OECD TG 421 study, because in the screening study findings on female reproductive tissues were only observed in the highest dose group (600 mg TeO_2/kg bw/d) which was clearly above the highest dose tested in the sub-chronic toxicity study (100 mg TeO_2/kg bw/d). That effects on female reproductive organs only occur at relatively high doses is also supported by the findings of a subacute (28-day) rat study with tellurium dioxide which described '*moderate diffuse epithelial atrophy in the vagina*' in two of four high dose (600 mg/kg bw/d) females (ECHA Dissemination, 2018).

Whether the effects on reproduction observed in the screening study are (partially) secondary to general toxicity is a matter of discussion. However, as outlined above, effects e.g. on 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. Additional information, e.g. measurements on hormone levels, which might provide information on endocrine imbalances, is missing. Mechanistic investigations performed in the context of tellurium-induced neuropathy revealed that tellurium interferes with cholesterol synthesis (Harry et al., 1989; Wagner et al., 1995). As cholesterol is a precursor of steroidal hormones there is some suspicion that tellurium might interfere with the endocrine system. This could also be an explanation for the observed disturbances of the oestrus cycles of HD-females which were characterised by persistent dioestrus. However, experimental verification of this interrelation is missing.

In summary, effects on fertility were observed in the HD, which already induced marked maternal toxicity (including lethality) but also (to a lesser extent) in the MD where only less severe maternal toxicity was observed. Effects on male reproduction were not observed. These data point to effects on female fertility. This is underlined by the observation that tellurium dioxide causes structural changes in female reproductive organs, an effect which is considered as substance related as well as the influence on the number of corpora lutea. Additionally, mechanistic investigations point to a possible interference of tellurium with the synthesis of steroidal hormones, however direct hormone measurements have not been investigated yet.

10.10.3 Comparison with the CLP criteria

There are no epidemiological data to support classification of tellurium dioxide in Category 1A.

There is only an oral OECD TG 421 screening study in rats available for tellurium dioxide or the read-across substance tellurium. Experimental data from this screening study provide clear evidence of adverse effects on sexual function and fertility in rats treated with tellurium dioxide. Mating and fertility indices were decreased in HD females. Additionally, gestation indices for MD and HD females were decreased and gestation length was increased in the MD. Non-pregnant females of the HD revealed a decrease or no corpora lutea and no implantation sites at necropsy. Oestrus cycles of HD-females were characterised by persistent dioestrus. Additionally, atrophy of female reproductive tissues was observed in HD females. Although it cannot be excluded that some of the effects observed are secondary to the toxicity (lethality) observed especially in HD females, effects like reproductive organ atrophy, influence on number of corpora lutea and oestrus cycle are considered as substance related and therefore relevant for classification. Additionally, effects on reproduction were also observed in the MD where no severe toxicity was observed.

The mechanism of action underlying the effects on sexual function and fertility is not clarified. However, there is no evidence for a species specific mechanism. Especially the mechanism for the inhibition of cholesterol synthesis (see below, sections 10.10.4 and 10.10.5) by inhibition of squalene epoxidase is also regarded as relevant for humans. Therefore, the effects observed in rats are regarded as relevant for humans.

In the absence of a clear indication that the fertility effects are secondary to maternal toxicity, especially in the MD group, and considering the effects are severe and substance related, the effects are regarded as relevant for classification. Considering the effects were dose-dependent and there are no reasons to question their relevance to humans, classification in Category 1B seems to be more appropriate than Category 2.

In summary, relevant and severe effects on sexual function and fertility have been observed in an OECD TG 421 screening study. The reproductive effects observed occurred at doses which also elicited severe general toxicity up to mortality. However, a) effects on sexual function and fertility were also observed at doses causing no 'marked systemic toxicity', b) substance related effects on reproduction occurred, and c) due to mechanistic data available for the read-across substance tellurium a direct influence of tellurium dioxide on sexual hormones cannot be excluded. Therefore, classification for effects on sexual function and reproduction in Category 1B is proposed.

10.10.4 Adverse effects on development

Table 22: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Prenatal Developmental Toxicity Study Not according to OECD TG 414, but examinations were similar to guideline GLP: no information Female Wistar rats (10 animals/dose group) RL2 (according to registration dossier and the authors of this document)	Tellurium dioxide (Purity: 99.99%) 0, 10, 100, 500, 1000 µmol TeO_2/kg bw/d (corresponding to 0, 1.6, 16, 80, 160 mg TeO_2 /kg bw/d) from GD 15 to GD 19 GD^+ 20: caesarean section Vehicle: olive oil Subcutaneous application	Dams: NOAEL: 16 mg TeO_2/kg bw/d (100 µmol/kg bw/d: effects at the highest dose group were weight loss, centrolobular fatty changes in the liver and 40% lethality). Offspring: NOAEL: 1.6 mg TeO_2/kg bw/d (10 µmol/kg bw/d most prominent effects were hydrocephalus (already 100% at 16 mg/kg bw/d), additionally edema, exophthalmia, ocular haemorrhage, umbilical hernia, undescended testis and small kidneys followed by increased fetal mortality in the two highest doses at GD20 (11% and 81% at 500, 1000 µmol TeO_2/kg bw/d, respectively) Remarks: In parallel a pair fed study was performed. Food consumption was measured for tellurium dioxide exposed rats which received 500 µmol/kg bw/d and had unlimited access to feed. In two pair-fed groups, which were bred one day later and received only vehicle or tellurium dioxide 500 µmol/kg bw/d, the rats received the same amount of feed as the rats of the ad-libitum 500 µmol/kg bw/d group. All tellurium dioxide exposed foetuses revealed hydrocephalus as most prominent effect. However, no such effects were observed in pair-fed control animals, indicating that not reduced food consumption was responsible for the effects observed in offspring of treated mothers. Furthermore, edema, exophthalmia, ocular hemorrhage, umbilical hernia, undescended testes and small kidneys was observed in all exposed litters.	(Perez-D'Gregorio and Miller, 1988) also reported in (ECHA Dissemination, 2018) (Perez-D'Gregorio et al., 1988) also reported in (ECHA Dissemination, 2018)
Reproduction / Developmental Toxicity Screening Test OECD TG 421	Tellurium dioxide (information on purity: see confidential annex) 0, 25, 120 and 600 mg TeO_2/kg bw/d,	Effects on parental animals see section 10.10.1 Offspring: LOAEL: 25 TeO_2 mg/kg bw/d (increased pup mortality at all dose groups) 600 mg/kg bw/d: no live pups	NN, 2013 reported from (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Deviations: no GLP: yes Male/female Wistar rats 12 animals per sex and dose group RL1 (according to registration dossier and the authors of this document)	Exposure: Males were dosed for 28 days (14 days pre-mating and 14 days mating/post-mating). They were sacrificed afterwards. Females were exposed 14 days pre-mating, for up to 14 days of mating (1:1), throughout gestation and up to day 4 of lactation, which was the day before necropsy. Application via gavage, 7 days/week Vehicle: 1 % (v/v) methyl cellulose solution	120 mg TeO_2/kg bw/d: 33/137 stillborn pups, 28/137 pups found dead but born alive (positive floating test), 39 cannibalised pups, and 65 were not nursed, more male than female pups died between PND0-PND4 25 mg TeO_2/kg bw/d: no effect on number of live born pups (148/173), 33 pups did not suckle, on PND4 the survival index was 75 % and therefore below the normal control range The mean litter weights on PND 0, pups body weight evaluated on PND 0 for all pups or per litter were decreased in all dose groups. Pup body weight on PND 4 and body weight gain was similar to the control in the Low and Mid dose animals. Total litter weights were below the normal control range in the Mid dose group on PND 0 and 4, and in the Low dose group at PND 0. The observed differences are probably a consequence of pup mortality, without an effect on the growth of survivors. At cross-pathology test item-related gross changes were observed in the cranium region and skin/subcutis in the High Dose group pups (two litters affected): absence of cranial region of the head with reduced brain size, covered by skin (n=4 pups); whole body subcutaneous gelatinous material in 16 found dead pups.	
Prenatal Developmental Toxicity Study Similar to OECD TG 414 Deviations: no GLP: yes Female Crl COBS CD (SD) BR rats (32-33 animals/dose group) RL2 (according to registration dossier and the authors of this document)	Read-across substance tellurium (Purity: 99.99%) 0, 30, 300, 3000, 15000 ppm Te (corresponding to 0, 1.9, 18, 173, 579.4 mg Te/kg bw/d mg/kg bw/d; would correspond to about 0, 2.4, 22.5, 216.4, 724.7 mg TeO_2/kg bw/d)* from GD 6 to GD 15 GD 20: 2/3 of the females underwent caesarean section, ½ of the foetuses were examined for soft tissue anomalies and ½ for osseous skeletal status; 1/3 of the dams delivered naturally;	<u>Dams:</u> NOEL: 1.9 mg Te/kg bw/d (reduced feed consumption, reduced body weight gain during exposure period which recovered after cessation of exposure, no maternal death) <u>Offspring:</u> NOAEL: 18 mg Te/kg bw/d (skeletal and soft tissue malformations, primarily hydrocephali at 173 and 579.4 mg Te/kg bw/d, number of pubs surviving 7 days reduced at highest dose) No. (%) of foetuses with dilated lateral ventricles: 1 (0.7); 0 (0); 1 (0.7); 11 (8.3); 67 (54.9) at 0, 30, 300, 3000, 15000 ppm Te, respectively); No. (%) of litters with dilated lateral ventricles: 1 (4.6); 0 (0); 1 (4.8); 3 (14.3); 17 (85) at 0, 30, 300, 3000, 15000 ppm Te, respectively) (%) litters/foetuses with variations: 18.2 (2.1); 35.0 (2.9); 28.6 (3.2); 57.1(10.6); 100 (40.6) at 0, 30, 300, 3000, 15000 ppm Te, respectively)	(Johnson et al., 1988) also reported in (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	foetuses and dams were sacrificed on PND 7. Application via diet		
Prenatal Developmental Toxicity Study Similar to OECD TG 414 Deviations: no GLP: yes Female New Zealand white rabbits (17 animals/dose group) RL2 (according to registration dossier and the authors of this document)	Read-across substance tellurium (Purity: 99.99%) 0, 17.5, 175, 1750, 5250 ppm Te (corresponding to 0, 0.7, 7, 70, 210 mg Te/kg bw/d mg/kg bw/d; would correspond to about 0, 0.9, 8.7, 87.6, 262.7 mg TeO_2/kg bw/d)** from GD 6 to GD 18 GD 29: all females underwent caesarean section, all foetuses were examined for soft tissue anomalies and thereafter for skeletal variations Application via diet	Dams: NOAEL: 7 mg Te/kg bw/d (reduced feed consumption, reduced body weight gain during exposure period which recovered after cessation of exposure, soft or liquid feces, alopecia, thin appearance, and/or decreased motor activity, no maternal death up to highest dose) Offspring: NOAEL: 70 mg Te/kg bw/d (HD: decreased fetal body weights, increased incidence of foetuses or litters with variations, malformations including hydrocephalus and with reversible delays in ossification, no individual numbers provided: 'There were low incidences of hydrocephalus, enlarged and/or irregularly shaped anterior fontanelle, incomplete ossification of, or small holes in, the frontals and parietals; frontals with thickened ossification; umbilical hernia; fused pulmonary artery and aorta; asymmetric and/or irregularly shaped and/or fused sternebrae; and thickened areas in the ribs in foetuses of high-dosage pregnancies.'; No. (%) of foetuses with abnormalities: 3 (6.7); 6 (5.1); 4 (6.0); 2 (1.8); 11 (11.8) at 0, 17.5, 175, 1750, 5250 ppm Te, respectively); No. (%) of litters with abnormalities: 2 (22.2); 5 (33.3); 2 (25); 1 (7.1); 6 (46.2) at 0, 17.5, 175, 1750, 5250 ppm Te, respectively)	(Johnson et al., 1988) also reported in (ECHA Dissemination, 2018)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Long Evans rats (5-11 dams per dose group and gestation day; 2-3 dams per control group and gestation day) RL4 (according to registration	Read-across substance tellurium (Purity: not provided) 13 mg Te/kg (would correspond to about 16.3 mg TeO_2/kg) Single application on gestation days 7, 8, 9, 10, 11, 12, or 13 Vehicle: olive oil (suspension) Dams were allowed to deliver and offspring observed till PND 10; sacrifice on PND 10 and fixation of offspring in Bouin's	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 13 mg Te/kg (hydrocephalus in offspring of animals treated on GD 9 (14 of 75 (18.6%) offspring) or GD 10 (10 of 32 (31%) offspring); one offspring with hydrocephalus in the group treated on GD7 (1 of 33 (3%) offspring) and one in an offspring of the control group (1 of 94 (1.1%) offspring), but not in offspring of dams treated on any other day of gestation; no other malformations observed; fetal resorptions were also observed, but examinations for uterine resorption sites were only performed in animals which failed to deliver by GD 22 (2/10, 3/8, 0/11, 1/6, 1/7, 0/5, 1/5 dams treated on GD 7, 8, 9, 10, 11, 12, 13, respectively)	(Agnew and Curry, 1972) also reported in (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
dossier and the authors of this document)	solution, examination for hydrocephalus (increased ventricular dilatation was classified as hydrocephalus) and other defects No information on maternal toxicity Application intramuscular		
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (32 dams per dose group, 16 dams in the control group) RL4 (according to the authors of this document)	Read-across substance tellurium (Purity: not provided) 3300 ppm Te (165 mg Te/kg bw/d[#] (would correspond to about 206 mg TeO_2/kg bw/d) Application throughout gestation' Dams (n=10) were allowed to deliver, foetuses were examined for hydrocephali No information on maternal toxicity Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 165 mg Te/kg bw/d (Hydrocephali were observed in 8/10 litters 4-5 days after birth, 47% (36/77) of all foetuses developed hydrocephalus, with up to 100% of all foetuses of a litter) Remark: No hydrocephalus was observed in preliminary experiments with two groups of four pregnant rats which received 1250 or 2500 ppm Te.	(Agnew et al., 1968)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Long Evans rats (> 100 dams, no further information)	Read-across substance tellurium (Purity: not provided) 500, 1250, 2500 ppm Te (25, 62.5, 125 mg Te/kg bw/d[#]; would correspond to about 31, 78, 156 mg TeO_2/kg bw/d) 'fed during pregnancy', dams of the high dose received normal diet	Dams: NOAEL 125 mg Te/kg bw/d (no detailed information provided, but stated that they behaved normally, tolerated the diet well and delivered on schedule) Offspring: LOAEL 25 mg Te/kg bw/d (100% hydrocephali in the highest dose group and 60-90% in the mid dose group, at the low dose group only a part of the litters were affected (60% according to Duckett, 1971); hydrocephali detectable immediately after birth; new-borns appeared smaller than controls; all offspring died within the first month after birth; no detailed examination of the foetuses for other endpoints)	(Garro and Pentschew, 1964) also reported in (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
RL4 (according to registration dossier and the authors of this document)	3-5 days before delivery Dams were allowed to deliver and offspring were examined for the occurrence of hydrocephali Application via diet		
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (30 dams in treatment group, 20 dams in test group) RL4 (according to registration dossier and the authors of this document)	Read-across substance tellurium (Purity: not provided) 3000 ppm Te (150 mg Te/kg bw/d#; would correspond to about 188 mg TeO_2/kg bw/d) fed 'every day of gestation' Dams were allowed to deliver and offspring were examined for the occurrence of hydrocephali Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 150 mg Te/kg bw/d (twenty-four of the female rats fed tellurium gave birth to litters. 20 of the rats gave birth to litters in which all the animals were hydrocephalic, 4 gestating rats gave birth to normal offspring. The hydrocephalus was non-obstructive in type for the first few days, after which obstructions appeared. Most of the animals died by the end of the second week. Only 61 of the 207 hydrocephalic rats born alive were still alive at the age of 10 days and only 44 survived till the age of 1 year.)	(Duckett, 1971) also reported in (ECHA Dissemination, 2018)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (20 dams in treatment group, 20 dams in test group) RL4 (according to	Read-across substance tellurium (Purity: not provided) 3000 ppm Te (180 mg Te/kg bw/d as calculated by the authors of the publication; would correspond to about 225 mg TeO_2/kg bw/d) fed 'every day of gestation' On GD 13 and 15 foetuses (number not specified) were	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 180 mg Te/kg bw/d (morphological anomalies in the cells in the ependymal layer of the treated foetuses: plasmalemma was without microvilli and the number of mitochondria was 'greatly diminished'; mitochondria 'were often abnormal, smaller and darker than normal and showed distortion of cristae')	(Duckett, 1970) also reported in (ECHA Dissemination, 2018)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
registration dossier and the authors of this document)	removed via abdominal wall; after closing the wall the dams were allowed to deliver; Only foetuses of Te fed animals who eventually gave birth to hydrocephalic animals, and foetuses of similar age control rats, were examined. Application via diet		
Developmental toxicity study No guideline followed Deviations: not applicable GLP: no data Female rats, strain not provided (20 animals/group) RL4 (according to registration dossier and the authors of this document)	Read-across substance tellurium (Purity: not provided Diet with 2500 ppm Te (according to authors of the publication rats usually consumed 20 g of diet, i.e. 50 mg tellurium which corresponds to ca. 200 mg Te/kg bw/d; would correspond to about 250 mg TeO_2/kg bw/d) Group 1: Exposure during day 1-21 of gestation Group 2: exposure of 20 dams from GD 1 to 9 Group 3: exposure of 20 dams from GD 10 to 15 Group 4: exposure of 20 dams from GD 16 to 21 No information on maternal toxicity Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 200 mg Te/kg bw/d Group 1: 12/20 dams gave birth to litters with about 8 pubs, 6 out of 8 were hydrocephalic Group 2: no foetuses with hydrocephalus Group 3: 12/20 dams gave birth to hydrocephalic animals. Group 4: no foetuses with hydrocephalus Remark: In a second experiment 21 groups of 5 dams received single doses of 200 mg Te/kg bw/d via diet on different days during gestation. Three animals died and 71 gave birth to an average of 8 offspring. None of the offspring had a hydrocephalus. No further details of results provided	(Duckett et al., 1971) also reported in (ECHA Dissemination, 2018)

[+] GD = gestation day

* calculated by the authors for GD 11-15; corresponding values for GD 6-10 were 0, 2.2, 19.6, 165.6, 633 mg/kg bw/d

** only the mg/kg bw/d value for the second highest dose group has been provided by the author, the other values have been calculated by linear extrapolation to the other doses

Calculated by using the standard factors as provided in Table R. 8-17 of the Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, November 2012 (ECHA, 2012)

Table 23: Summary table of human data on adverse effects on development

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no human data available				

Table 24: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Investigation of tellurium-induced neuropathy no guideline followed Deviations: not applicable GLP: no information Male Long Evans rats (weaned at PND 17, rats from 6 litters, number not provided) RL2 (according the authors of this document)	Read-across substance tellurium (Purity: 99%) 12500 ppm Te (625 mg Te/kg bw/d*; about 782 mg TeO_2/kg bw/d) Exposure PND 20 – 27 Examinations: morphologic analysis, biochemical analysis of myelin specific P_0 protein, *in vitro* analysis of myelin lipids synthesis in Schwann cells isolated from treated and control rats	Mechanistic study, investigation on the tellurium-induced neuropathy model in rats	Te treated rats develop a transient neuropathy characterized by synchronous demyelination of peripheral nerves; maximal (25%) sciatic nerve demyelination after 5 days of treatment, thereafter remyelination starts; after 30 days metabolic and morphologic alterations were no longer apparent; authors of the publication discuss that Te probably inhibits myelin synthesis by inhibition of squalene epoxidase.	(Harry et al., 1989)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
	Application via diet			
Investigations on the mechanism of tellurium induced neuropathy *In vivo* and *in vitro* studies, not following any guideline	Read-across substance tellurium (Purity: not provided) 11000 ppm Te (550 mg Te/kg bw/d*; about 688 mg TeO_2/kg bw/d) Exposure PND 20 – 23 Application via diet	Mechanistic study, investigation on the tellurium-induced effect on squalene epoxidase in sciatic nerves and liver	Inhibition of cholesterol synthesis and accumulation of squalene in different tissues after tellurium feeding. Incubation of radioactive precursors of cholesterol with sciatic nerve segments or liver slices in the presence of tellurite resulted in an accumulation of squalene. Indications for different susceptibilities of liver and sciatic nerve towards tellurium induced inhibition of cholesterol synthesis.	(Wagner et al., 1995)

* Calculated by using the standard factors as provided in Table R. 8-17 of the Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, November 2012 (ECHA, 2012)

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

There are no human studies addressing adverse effects on development of tellurium or tellurium dioxide available.

Only one developmental toxicity study with tellurium dioxide could be identified (Perez-D'Gregorio and Miller, 1988). In this study with subcutaneous injection which was performed similar to OECD TG 414 adverse effects were observed in foetuses already at a dose of 16 mg TeO_2/kg bw/d, which did not cause maternal toxicity. The most prominent effect in foetuses were hydrocephalus (already 100% at 16 mg/kg bw/d), additionally edema, exophthalmia, ocular haemorrhage, umbilical hernia, undescended testis and small kidneys and increased fetal mortality in the two highest dose groups were observed (Table 25). Maternal animals showed adverse effects at doses equal or above 80 mg TeO_2/kg bw/d: weight loss, centrolubular fatty changes in the liver and 40% lethality in the highest dose group (160 mg TeO_2/kg bw/d).

Table 25: Overview of the results from the PNDT by Perez-D'Gregorio and Miller (1988)

Dose level (mg/kg bw/d)	0	1.6	16	80	160
Maternal mortality	0/10	0/10	0/10	0/10	4/10
Early/late resorptions	5/1	5/0	3/1	4/1	4/1
No of live/dead foetuses	120/0	112/0	114/0	120/15	12/51

Undescended testis#	2/54	2/51	18/52*	36/51*	29/33*
Hydrocephalus#	0/120	0/120	114/114	135/135	63/63
Edema#	0/120	0/120	114/114	135/135	63/63

* Significantly different from control group ($p \leq 0.01$)

#: Information taken from Figure 4 of the publication

To correct for a possible effect of lower maternal food intake on birth defects, a pair fed study was performed for animals of the second highest dose group (80 mg TeO_2/kg bw/d) (Perez-D'Gregorio et al., 1988). As the effects observed in the group with feed access ad libitum and pair-fed animals were comparable it can be concluded that changes in maternal food consumption are not the primary cause of the fetal malformations.

In a reproductive screening study according to OECD TG 421 Wistar rats were exposed to 0, 25, 120 or 600 mg TeO_2/kg bw/d by gavage. The most prominent effect observed in pups was the increased mortality which was significant in all dose groups (**Table 26**). Effects on weight and weight gain of pups were probably due to the increased maternal toxicity rather than an effect on the growth of the viable pups. Further, test-item related gross changes were observed in the cranium region and skin/subcutis in the high dose group pups (two litters affected): absence of cranial region of the head with reduced brain size, covered by skin (n=4 pups); whole body subcutaneous gelatinous material in 16 found dead pups. No hydrocephalus was observed. This might be due to the high mortality observed, possibly due to the bolus effect due to gavage.

Effect levels for the pups were higher than the effect levels for the dams in these two studies with tellurium dioxide; however, the effects observed in dams are regarded as indicative of slight toxicity only (reduced feed intake, reduced weight gain, no mortality). Therefore, the effects on pups are probably not secondary to the effects in dams.

Table 26: Overview of the results from the reproductive screening study, (NN, 2013)

Dose level (mg/kg bw/d)	**0**	**25**	**120**	**600**
Maternal mortality	0/12	0/12	0/12	5/12
Fertility index	100%	100%	100%	63% (3/11 non-pregnant)
Gestation index	92%	100%	67%	0%
No of dead/total pups on PND 0	13/160* (14/162))	25/173	33/137	19/19
Number of pups alive on PND 4	147* (147)	127	53	0
Absense of cranium, small brain/examined pups	0/12	0/30	0/45	4/16
Whole body subcutaneous gelatinous material/examined pups	0/12	0/30	0/45	16/16

* one litter with < 5 implantation sites not considered (numbers considering all liters)

Besides these investigations with tellurium dioxide, several developmental toxicity studies are available for the read-across substance tellurium. There are two reliable PNDT studies, one in rats and one in rabbits performed similar to guidelines (Johnson et al., 1988). Both studies describe similar findings as Perez-D'Gregorio and Miller (1988) with hydrocephali being the major malformation in rats accompanied by increased pup mortality in the highest dose group. These effects occurred at doses that elicited only slight toxicity in dams. In the rabbit study, also hydrocephali have been observed besides other findings like decreased foetal body weights, increased incidence of variations and delays in ossification. The incidences of hydrocephali were 'low', a detailed documentation of the results in rabbits is missing in the publication. But this study confirms the occurrence of this typical tellurium induced malformation in a second species.

Additionally, there are several other publications, which in a consistent manner describe the induction of adverse effects on rat foetuses after intrauterine exposure to tellurium, especially the induction of hydrocephali. Most of these studies have limitations, including that the investigations were only performed with one dose group, that the investigation depth was limited (focus mainly on the induction of hydrocephali), and that the documentation is inadequate. Nevertheless, these studies provide valuable information, e.g. on the target period for the induction of hydrocephalus, which is between GD9-15. Neither exposure before GD9 nor after GD15 resulted in the induction of hydrocephali. At sufficiently high doses, single exposure was sufficient for the induction of hydrocephali. Information on the day of appearance is somewhat contradictory. Whereas some authors detected this malformation immediately after birth (Garro and Pentschew, 1964), others described that it was not detectable before PND 4 (Agnew et al., 1968).

Another well-known effect of tellurium on the developing rat is the induction of a transient neuropathy characterized by synchronous demyelination of peripheral nerves (Harry et al., 1989). This effect can reproducibly be induced by treatment of weanling rats. The effect is reversible after cessation of treatment. The molecular mechanisms behind this transient neuropathy have been investigated by several authors (Berciano et al., 1998; Calle et al., 1999; Toews et al., 1991; Toews et al., 1997; Toews et al., 1990; Wagner et al., 1995). Critical for the induction of the neuropathy is a selective block of cholesterol synthesis, specifically by inhibiting the squalene epoxide reaction, which converts squalene to lanosterol. Consequently, the cholesterol synthesis and myelin formation is inhibited (Toews et al., 1990). According to the *in vitro* investigations of Wagner et al. (1995) the active metabolite responsible for squalene epoxidase inhibition is probably tellurite ($(TeO_3)^{2-}$).

10.10.6 Comparison with the CLP criteria

There are no epidemiological data to support classification of tellurium dioxide in Category 1A.

Developmental toxicity has consistently been observed in all available developmental toxicity studies performed with tellurium dioxide and the read-across substance tellurium. There are two studies performed with tellurium dioxide, one study similar to OECD TG 414 with subcutaneous injection of rats and a screening study in rats according OECD TG 421 with application via gavage. In the developmental toxicity study severe effects were observed in foetuses. In the lowest effect dose (16 mg TeO_2/kg bw/d) all foetuses exposed during gestation developed hydrocephalus at a dose which did not induce adverse effects in dams. Investigations in a pair feeding study additionally revealed that also at a higher dose (80 mg TeO_2/kg bw/d), the effect on the pups was not due to the weight loss observed in dams treated with tellurium dioxide. In the OECD TG 421 screening study tellurium dioxide caused increased pup mortality in all dose groups and even at doses which did not cause toxicity in dams. Therefore, the effects observed in pups are not considered secondary to maternal toxicity.

These findings for tellurium dioxide are supported by two developmental toxicity studies in rats and rabbits with the read-across substance tellurium. Again, induction of hydrocephalus and increased pup mortality were observed in rats. Also rabbits developed hydrocephalus, but to a lesser extent than rats. Effect levels for the pups were higher than the effect levels for the dams in these two studies, however, the effects observed in dams are regarded indicative of slight toxicity (reduced feed intake, reduced weight gain, no mortality). Therefore, the effects in the pups are probably not secondary to the effects in dams.

Several other studies with tellurium confirm the finding that tellurium induces hydrocephali in rats. However, no information is available if the effects in the pups occur at doses which are already toxic to the

dams as most of these studies did not report the effects in dams or did not clearly state that there are no effects in dams.

Additional studies reveal that tellurium not only induces effects on development when provided during gestation but also when administered to weanling rats, which develop the so-called tellurium neuropathy which is characterised by a demyelination of peripheral nerves.

The mechanism of action underlying the foetotoxic effects, especially the development of hydrocephalus is not clarified. However, there is no evidence that this mechanism is species specific. Therefore, the effects observed in rats and rabbits are regarded as relevant for humans.

The mechanisms underlying the induction of tellurium induced reversible neuropathy, *inter alia* inhibition of squalene epoxidase, has been analysed. The effects observed in rats are regarded as relevant for humans, as the cholesterol synthesis is highly conserved between species.

In summary, there is consistent evidence from experimental studies with rats and rabbits for both tellurium dioxide and the read-across substance tellurium, that tellurium dioxide causes developmental toxicity after gestational exposure or exposure to weanling rats at doses not or only slightly toxic to dams. Most relevant effects caused by tellurium dioxide are severe malformations, i.e. hydrocephalus, and pup lethality. Considering these effects are severe, consistent, and relevant for humans, classification for developmental toxicity in Category 1B is proposed.

10.10.7 Adverse effects on or via lactation

Table 27: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Investigation of effects via lactation No guideline followed GLP: no information Female Wistar rats (n=2 females in the treatment and control group for each examination day; n=5 pups per group and investigation time point)	Read-across substance tellurium (Purity: not provided) 0, 1.25% in diet (corresponding to 0, 625 Te mg/kg bw/d *; would correspond to about 782 mg TeO_2/kg bw/d) from PND 0 to PND 7, 14, 21, or 28; exposure from PND0-17 was vial milk, thereafter via Te-containing diet	Dams: NOAEL: 625 mg Te/kg bw/d (garlic odour odour (within 2-3 days after start of exposure), greyish skin discoloration (after 7 days), no other clinical effects occurred) Offspring: LOAEL: 625 mg Te/kg bw/d (garlic odour (within 2-3 days after start of exposure) in offspring, skin discoloration (after 7 days), the following signs of toxicity developed within two weeks from start of exposure: lethargy, hind limb paralysis, incontinence, slow weight gain and smaller size; microscopic examination of nerve tissue revealed hypomyelination of the optic nerve accompanied by slight myelin degeneration; myelin degeneration and Schwann cell degeneration in sciatic nerve; effects on sciatic nerve were detectable at all ages of examination, hypomyelination of the optic nerves was demonstrated at 14, 21, and 28 days of age)	(Jackson et al., 1989)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
RL3 (according to the authors of this document)	examinations of pups: light and electron microscopic investigations of spinal cord, optic nerve and sciatic nerve; including measurement of myelin density, myelin sheath thickness and myelinated axon diameter Application via diet		

* Calculated by using the standard factors as provided in Table R. 8-17 of the Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, November 2012 (ECHA, 2012)

Table 28: Summary table of human data on effects on or via lactation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable since no human data available				

Table 29: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Not applicable				

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

There are no human data available with respect to effects via lactation.

There is only one experimental study in rats available, which investigated effects of the read-across substance tellurium via lactation. Offspring of dams exposed via diet towards tellurium showed clinical signs of toxicity already a few days after start of exposure via breast milk. The microscopic examination of nerve tissues of the offspring revealed typical effects of tellurium intoxication like hypomyelination, myelin degeneration and Schwann cell degeneration. Depending on the nerve tissue investigated, these effects were detectable at all time points or at the three last time points of investigation. The first time point for investigation was on PND 7, i.e. at a time when exposure of the pups occurred only via mother milk. Effects observed at later time points might have been caused by both, exposure via mother milk and/or exposure via diet of weanling rats.

Only one dose group was used and no information on test substance purity was provided. Further, only n=2 pups were investigated at the indicated time points for the different effects. No analytical measurement of Te concentration in the milk was performed. Due to these shortcomings the study is regarded as not reliable (RL3).

Further doubts on the validity of the study arise from the fact that no toxicity was reported in dams at doses equivalent to 782 mg tellurium dioxide/kg bw/d whereas doses equal or higher than 120 mg tellurium dioxide/kg bw/d caused effects on clinical signs, body weight, food intake and histopathology in rats of the OECD 421 study. Also Johnson et al described toxic effects at much lower doses in rats exposed via diet. Therefore, although the reported effects are considered relevant and specific to Tellurium, no final conclusions can be drawn on basis of this study due its limitations.

10.10.9 Comparison with the CLP criteria

There are indications of adverse neurotoxic effects after exposure via breast milk. Although the observed effects are specific for tellurium, due to severe deficiencies of the only available study, no firm conclusion can be drawn. In the absence of relevant and reliable studies in humans or experimental animals on possible effects on or via lactation the criteria are not applicable and no classification for tellurium dioxide for effects on or via lactation is proposed.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

In the absence of human data and due to the effects observed in experimental animals it is proposed to classify tellurium dioxide for effects on sexual function and fertility.

Therefore classification for effects on sexual function and fertility (Cat. 1B, H460F) is warranted for tellurium dioxide.

In the absence of human data and due to the effects observed in experimental animals it is proposed to classify tellurium dioxide for effects on development.

Therefore classification for effects on development (Cat. 1B, H460D) is warranted for tellurium dioxide.

In the absence of relevant and reliable studies no classification is proposed for effects of tellurium dioxide on or via lactation due to a lack of data.

Therefore no classification for effects on or via lactation is warranted for tellurium dioxide.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

According to the DS there are no studies in humans addressing adverse effects on sexual function and fertility. The DS presented two recent studies in animals dealing with the impairment of fertility or mammalian development after exposure to TeO_2, one Reproduction/Developmental toxicity screening study in rats (OECD TG 421, Anonymous, 2013c) and a sub-chronic study in rats (OECD TG 408, Anonymous, 2017). According to the DS, relevant and severe effects on sexual function and fertility have been observed in an OECD TG 421 screening study at doses, which elicited severe general toxicity, up to mortality, but also at doses without marked systemic toxicity. Therefore, the DS was of the opinion that classification as Category 1B for adverse effects on sexual function and fertility is justified for tellurium dioxide.

In the Reproduction/Developmental toxicity screening study from 2013, according to GLP and OECD TG 421 (Anonymous, 2013c), twelve Wistar rats/sex/dose were exposed via gavage to tellurium dioxide at 0, 25, 120 and 600 mg/kg bw/d 7 days/week. Males were exposed for 28 days (14 days pre-mating and 14 days post-mating) and were sacrificed afterwards. Females were dosed 14 days pre-mating, up to 14 days of mating, throughout gestation and up to day 4 of lactation. In the P0 generation systemic effects occurred at 120 (mid dose, MD) and 600 (high dose, HD) mg/kg bw/d. In HD females pronounced mortality was observed. Five females died between days 14 and 45, one female died due to a gavage accident, one female died on day 13 of the mating period. In HD animals, clinical signs like decreased activity, liquid faeces, hunched back, laboured respiration, lethargy, piloerection and red liquid from mouth and vulva were noted. In MD and HD animals, bw, bw gain and food consumption were decreased in males and females, resulting in terminal bw in males about 7 and 14% lower than controls, and in females about 5 and 11% lower (on day 14 of exposure). The NOAEL for systemic effects is 25 mg/kg bw/d.

In HD females, the mating and fertility indices were decreased to about 73% and 63%. In MD and HD, females the gestation index was decreased (92, 100, 67, 0% in ctrl, LD, MD, HD, respectively). Four out of six HD females were non-pregnant with reduced or no corpora lutea and no implantation sites. Oestrus cycle of HD females was characterised by dioestrums. The gestation period in MD females was statistically significantly prolonged by 0.7 days (Control: 22.73 days, MD: 23.42). The two females of the HD group that delivered had a mean duration of pregnancy of 24 days (+1.3 days).

Histopathological observations detected atrophy of ovary, uterus and vagina in 4/5 dead HD females, a moderate vacuolation of corpora lutea and pigment deposits in the right ovary of 1/5 females. In other HD females, also histopathologic changes of reproductive organs as well as on kidney, liver and thymus (histopathology only in control and HD animals) were observed. No adverse effects on male reproductive organs were observed.

The DS mentioned mechanistic studies (Harry *et al.*, 1989, Wagner *et al.*, 1995), which were conducted to clarify the mechanism of tellurium-induced neuropathy. In these studies, it was demonstrated that tellurium interferes with the squalene epoxidase, the enzyme catalysing the

first and rate limiting step of cholesterol synthesis. As cholesterol is a precursor for steroidal hormone synthesis, the DS indicated that there is some suspicion that tellurium could interfere with the endocrine system, which might explain the observed disturbance of hormonally regulated processes (oestrus cycle, duration of gestation). However, experimental verification is missing.

In a subchronic oral toxicity study in male Wistar rats according to GLP and OECD TG 408 from 2017, the animals were exposed via gavage to 0, 10, 30 and 100 mg/kg bw/d. No treatment related effects were observed at any dose group.

The DS mentioned that also in a rat 28-day study, which is also part of the registration dossier (Anonymous, 2013), effects on female reproductive organs were noted at 600 mg/kg bw/d; in 2 of 4 females, moderate diffuse epithelial atrophy of the vagina was noted. No further details on this study are presented in the CLH dossier.

Development

There are no studies addressing adverse effects of tellurium or tellurium dioxide on human development. The DS evaluated 9 developmental toxicity studies in rats and one study in rabbits. Two studies are performed with tellurium dioxide and eight with tellurium.

Based on the severe effects consistently seen in a pre-natal developmental toxicity study in rats (Perez-D'Gregorio & Miller, 1988) and a reproductive screening study in rats (Anonymous, 2013c) with tellurium dioxide and several prenatal developmental toxicity studies conducted with the read-across substance tellurium (Johnson *et al.*, 1988, Agnew & Curry, 1972, Agnew *et al.*, 1968, Garro & Pentschew, 1964, Duckett, 1971a, b, Duckett, 1970) in rats and rabbits (Johnson *et al.*, 1988), including doses with only slight or absent maternal toxicity, the DS proposed to classify tellurium dioxide as Repr. 1B; H360D.

Several studies with the read-across substance tellurium investigated different exposure durations and identified a time window, which is relevant for the induction of the main malformation, i.e. hydrocephalus. The relevant exposure period is from gestation day (GD) 9 to 15. Even single doses, if high enough, administered within this period resulted in the induction of hydrocephalus.

The studies with tellurium dioxide are summarised in the following table (modified).

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Prenatal Developmental Toxicity Study Similar to OECD TG 414 GLP: no information Female Wistar rats (10 animals/dose group) K2	Tellurium dioxide (Purity: 99.99%) 0, 10, 100, 500, 1000 µmol TeO_2/kg bw/d in olive oil (corresponding to 0, 1.6, 16, 80, 160 mg TeO_2/kg bw/d) from GD 15 to GD 19 GD 20: caesarean section Subcutaneous application	Dams: NOAEL: 16 mg TeO_2/kg bw/d (100 µmol/kg bw/d: effects at the highest dose group were weight loss, centrilobular fatty changes in the liver and 40% lethality). Foetuses: NOAEL: 1.6 mg TeO_2/kg bw/d (10 µmol/kg bw/d); most prominent effects were hydrocephalus (100% at 16 mg/kg bw/d), additionally oedema, exophthalmia, ocular haemorrhage, umbilical hernia, undescended testis and small	(Perez-D'Gregorio and Miller, 1988) also reported in (ECHA Dissemination, 2018)

		kidneys followed by increased foetal mortality in the two highest doses (11% and 81% at 500 and 1000 µmol TeO_2/kg bw/d, respectively) Remarks: In parallel a pair fed study was performed. All tellurium dioxide exposed foetuses revealed malformations, however, no such effects were observed in pair-fed control animals, indicating that reduced food consumption was not responsible for the effects.	
Reproduction / Developmental Toxicity Screening Test OECD TG 421 Deviations: no GLP: yes Male/female Wistar rats 12 animals per sex and dose group K1	Tellurium dioxide 0, 25, 120 and 600 mg TeO_2/kg bw/d Exposure: Males were dosed for 28 days (14 days pre-mating and 14 days mating/post-mating). They were sacrificed afterwards. Females were exposed 14 days pre-mating, for up to 14 days of mating (1:1), throughout gestation and up to day 4 of lactation, which was the day before necropsy. Daily application via gavage Vehicle: 1 % (v/v) methyl cellulose solution	Offspring: LOAEL: 25 mg TeO_2 /kg bw/d (increased pup mortality at all dose groups) 600 mg TiO_2 mg/kg bw/d: no live pups 120 mg TeO_2/kg bw/d: 33/137 stillborn pups, 28/137 pups found dead but born alive (positive floating test), 39 cannibalised pups, and 65 were not nursed, more male than female pups died between PND 0 and PND 4 25 mg TeO_2/kg bw/d: no effect on number of live born pups (148/173), 33 pups did not suckle, on PND4 the survival index was 75 % and therefore below the normal control range Total litter weights were below the normal control range in the MD group on post-natal days (PND) 0 and 4, and in the LD group at PND 0. The observed differences are probably a consequence of pup mortality, without an effect on the growth of survivors.	Anonymous, 2013c reported from (ECHA Dissemination, 2018)

K: Klimisch

The DS compiled maternal and foetal findings from the key developmental study with tellurium dioxide in the following table (Perez-D'Gregorio and Miller, 1988):

Dose level (mg/kg bw/d)	**0**	**1.6**	**16**	**80**	**160**
Maternal mortality	0/10	0/10	0/10	0/10	4/10
Early/late resorptions	5/1	5/0	3/1	4/1	4/1
No of live/dead foetuses	120/0	112/0	114/0	120/15	12/51
Undescended testis#	2/54	2/51	18/52*	36/51*	29/33*

Hydrocephalus#	0/120	0/120	114/114	135/135	63/63
Oedema#	0/120	0/120	114/114	135/135	63/63

* Significantly different from control group (p≤0.01); # information taken from Figure 4 of the publication

In a reproductive toxicity screening test from 2013 (Anonymous, 2013c), Wistar rats were exposed to Tellurium dioxide at dosages of 0, 25, 120 or 600 mg/kg bw/d via gavage. The test was performed according to OECD TG 421 (males exposed for 28 days before and after mating; females before gestation, and during gestation until PND4). The most prominent effect in pups was the increased mortality in all dose groups, reaching 100% in the top dose group. In the top dose group 5 out of 12 dams died. Fertility index was 63 %.

The most relevant effects are summarised in the table below.

Dose level (mg/kg bw/d)	**0**	**25**	**120**	**600**
Maternal mortality	0/12	0/12	0/12	5/12
Fertility index	100%	100%	100%	63%
Gestation index	92%	100%	67%	0%
No of dead/total pups on PND 0	13/160	25/173	33/137	19/19
Number of pups alive on PND 4	147	127	53	0
Absence of cranium, small brain/examined pups	0/12	0/30	0/45	4/16
Whole body subcutaneous gelatinous material/examined pups	0/12	0/30	0/45	16/16

Adverse effects on or via lactation

Effects of tellurium dioxide on lactation have not been studied. In a read across approach, the DS provided a non-guideline study with tellurium for the effects on lactation in rats (Jackson *et al.*, 1989). Female Wistar dams (2 per dose group) were exposed to 0 or 625 mg/kg bw/d from PND 0 to PND 7, 14, 21 or 28. Light and electron microscopic investigations of spinal cord, optic nerve and sciatic nerve; including measurement of myelin density, myelin sheath thickness and myelinated axon diameter were performed in pups.

Offspring of dams being exposed via diet showed clinical signs of toxicity already a few days after start of exposure via breast milk. The microscopic examination of nerve tissues of the offspring revealed typical effects of tellurium intoxication like hypomyelination, myelin degeneration and Schwann cell degeneration. Depending on the nerve tissue investigated, these effects were detectable at all time points or at the three last time points of investigation with PND 7 being the first time point. The transmission of tellurium to the offspring was demonstrated by the presence of garlic odour within 2-3 days and skin discolouration. Garlic odour and greyish discolouration of the skin was also seen in dams, but no other toxic signs were reported in dams.

The DS did not propose to classify for lactation due to doubts about the validity of the study. It was mentioned that only one rather high dose was tested with no information on purity of the test material, only two pups were tested at the indicated time points for the different effects and no analytical measurement of tellurium in milk was conducted. The DS further questioned the validity of the study because no toxicity was reported in the dams, despite the rather high dose applied (625 Te mg/kg bw/d), whereas in another dietary study (Johnson *et al.*, 1988) toxic effects were already seen at 18 mg/kg bw/d and in the reproductive screening study

using gavage application at 120 mg/kg bw/d. The DS classified the study as Klimisch 3.

Comments received during public consultation

One MSCA supported the read-across approach between tellurium dioxide and tellurium for reproductive toxicity.

One MSCA did not support classification as Repr. 1B; H360F because of increased mortality, which indicates severe toxicity of the substance and proposed to classify as Repr. 2 for fertility instead. Repr. 1B; H360D however was supported.

One company manufacturer and one industry association supported the classification as Repr. 1B; H360D, but without classification for fertility as the fertility observed effects might be secondary effects due to general toxicity.

No comments on lactation were submitted.

Assessment and comparison with the classification criteria

Sexual function and fertility

At the top dose of 600 mg TeO_2/kg 5 of 12 rats died, body weight was reduced by 11%, and fertility index was reduced to 63% (5 of 8 rats). Due to the high mortality at this dose level, effects on reproductive parameters cannot be properly evaluated. Changes in the gestation index and gestation length were observed at doses, which reduced body weight of the females by 5% and did not cause mortality (MD, 120 mg/kg). Histologically effects were noted at the lethal dose level, but corresponding data for the MD are missing (only control and HD animals were histopathologically examined in case no macroscopic findings were observed). RAC agrees with the DS that the known interference of tellurium squalene epoxidase and the resulting inhibition of cholesterol synthesis might lead to hormonal imbalance due to the dependence of steroid hormone synthesis on cholesterol. However, additional information on clinical chemistry, e.g. measurements on hormone levels, which might provide information on endocrine imbalances, is missing. It is further noted that the study authors did not consider the observed effects in the female reproductive organs as secondary to the observed general toxicity.

In order to allow for a better interpretation of the results an overview of the maternal toxicity is presented below.

No clinical signs were seen in control and LD, but at MD and HD, all animals had dark faeces. At the HD, considerable clinical signs like reduced activity, hunched back or piloerection was seen in females. The effects on female body weight and body weight gain are summarised in the following table.

***Table**: Female body weights in the OECD TG 421 study (Anonymous, 2013c).*

Body weight (%, compared to control)	LD (n = 12)	MD (n = 12)	HD (n = 2)
Day 14	- 4.3	- 4.7	- 11 *
GD 0	- 5.1	- 6.1	- 15.2 **
GD 7	- 5.3 *	- 7.8 **	- 14 **
GD 14	- 6.5 *	- 10 **	- 16.1 **
GD 20	- 6.9 *	- 13.3 **	- 19.8 **
PND 0	- 7.1 *	- 14.4 **	- 29.2 **

PND 4	- 7.8 *	- 18.3 **	- 30.2 **
Body weight gain (%, compared to control)	**LD (n = 12)**	**MD (n = 12)**	**HD (n = 2)**
Day 14 – GD 0	- 45.3	- 70.4	- 206.5
G 0 – GD 14	- 6.6	-18.9	-6.0
GD 7 – G 14	- 14.5 *	-25.1 **	-30.8 *
GD 14 – GD 20	- 8.4	- 25.3 **	-32.9 *
GD 0 – GD 20	- 9.5	- 23.8 **	- 26.5 **
GD 20 – PND 0	- 6.4	- 9.8	+11.9
PND 0 – PND 4	- 26.5	- 115.8	- 56.3

Statistically significant *: $p \leq 0.05$; ** $p \leq 0.01$
It is stated that changes in the LD were within the historical control range (historical control data not presented).

In summary, effects on fertility and histological changes of female reproductive organs were observed in the HD, which induced pronounced maternal lethality. As no histopathological examination of the MD female reproductive organs was performed it is not possible to exclude similar changes in the MD. In the original study summary, it is concluded that the observed atrophies were substance related and not secondary to the observed general toxicity.

It is further noted that a screening study is not equivalent to a generation study, as it uses fewer animals and the pre-mating exposure duration is only for two weeks. In addition, there is a rather large space between the MD of 120 mg/kg bw/d, where only minor maternal toxicity was observed and the HD of 600 mg/kg bw/d, which induced severe maternal toxicity and death. Relevant effects might have been observed if doses between MD and HD would have been tested. Furthermore, the test guideline recommends to histologically assess the organs of all animals affected by toxicity in the HD, but also the organs from animals in low and mid dose. Although the uterus, the ovaries and the vagina were affected in HD animals, no detailed histopathological analyses of these organs was performed in LD or MD animals.

Reduction of the gestation index in a small number of rats (4/12 animals with stillborns) and a slight increase of gestation length (+0.7 days), but no changes in the fertility index, were observed at the MD. Effects on male reproductive organs were not observed. Although data are not conclusive, they point to effects on female fertility. This is underlined by the observation that tellurium dioxide causes structural changes in female reproductive organs and leads to reduced numbers of corpora lutea.

Histological changes of the vagina were also seen in the top dose in a 28-day study (Anonymous, 2013d), which tested the same doses as the reproductive screening study (Anonymous, 2013c). In 2 out of 4 top dose females, moderate diffuse epithelial atrophy of the vagina was noted. Furthermore, in this study considerable toxicity was seen in the MD and HD, including one death in the HD females.

Human data on fertility and reproductive function are not available.

RAC concurs with the proposal by the DS that classification is justified for TeO_2 for adverse effects on sexual function and fertility. A reduction in gestation index as well as a prolonged gestation period was seen at doses, which did not cause severe general toxicity. However, there is no information on possible effects on reproductive organs at doses without severe general toxicity. Taking this into account, RAC considers that **classification for adverse effects on sexual function and fertility in category 2 is justified**.

Developmental toxicity

As there are no epidemiological data available for humans, classification of tellurium dioxide in Cat. 1A is not justified.

However, developmental toxicity has consistently been observed in all available developmental toxicity studies performed with tellurium dioxide and tellurium. Studies with tellurium dioxide are performed with subcutaneous injection or application via gavage. Even in the lowest dose in the developmental toxicity study, severe effects like hydrocephalus occurred in all foetuses without any effects in dams. The screening study revealed increased pup mortality already at doses, which did not cause toxicity in dams.

These findings are supported in a series of further studies with tellurium. Only two studies, one in rats and one in rabbits are considered reliable. In both studies hydrocephalus and increased pup mortality was observed. Additional studies date back to the 1960ies or 1970ies and details of the findings are often missing (e.g., most of these studies did not report the effects in dams or did not clearly state that there were no effects in dams). However, these studies investigated the time period relevant for the induction of hydrocephalus, one using the intra-muscular route of exposure. It could be demonstrated that even a single dose can induce hydrocephaly, if the dose is high enough and when applied within the relevant time window (GD 9 – 15). Studies with tellurium are summarised in the following table.

Reproductive Toxicity of Tellurium (supporting evidence for Tellurium dioxide)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Prenatal Developmental Toxicity Study Similar to OECD TG 414 Deviations: no GLP: yes Female Crl COBS CD (SD) BR rats (32-33 animals/dose group) K2	Tellurium (Purity: 99.99%) 0, 30, 300, 3000, 15000 ppm Te (corresponding to 0, 1.9, 18, 173, 579.4 mg/kg bw/d) from GD 6 to GD 15 GD 20: 2/3 of the females underwent caesarean section, 1 out of 2 of the foetuses were examined for soft tissue anomalies and ½ for osseous skeletal status; 1/3 of the dams delivered naturally; foetuses and dams were sacrificed on post-natal day (PND) 7. Application via diet	Dams: NOEL: 1.9 mg Te/kg bw/d (reduced feed consumption, reduced body weight gain during exposure period which recovered after cessation of exposure, no maternal death) Offspring: NOAEL: 18 mg Te/kg bw/d (skeletal and soft tissue malformations, primarily hydrocephalus at 173 and 579.4 mg Te/kg bw/d, number of pups surviving 7 days reduced at highest dose) No. (%) of foetuses with dilated lateral ventricles: 1 (0.7); 0 (0); 1 (0.7); 11 (8.3); 67 (54.9) at 0, 1.9, 18, 173, 579.4 mg/kg bw/d, respectively); No. (%) of litters with dilated lateral ventricles: 1 (4.6); 0 (0); 1 (4.8); 3 (14.3); 17 (85) at 0, 1.9, 18, 173, 579.4 mg/kg bw/d, respectively) % litters/foetuses with variations: 18.2 (2.1); 35.0 (2.9); 28.6 (3.2); 57.1(10.6); 100 (40.6) at 0, 1.9, 18, 173, 579.4 mg/kg bw/d, respectively)	(Johnson *et al.*, 1988) also reported in (ECHA Dissemination, 2018)

Prenatal Developmental Toxicity Study Similar to OECD TG 414 Deviations: no GLP: yes Female New Zealand white rabbits (17 animals/dose group) K2	Tellurium (Purity: 99.99%) 0, 17.5, 175, 1750, 5250 ppm Te (corresponding to 0, 0.7, 7, 70, 210 mg/kg bw/d) from GD 6 to GD 18 GD 29: all females underwent caesarean section, all foetuses were examined for soft tissue anomalies and thereafter for skeletal variations Application via diet	Dams: NOAEL: 7 mg Te/kg bw/d (reduced feed consumption, reduced body weight gain during exposure period which recovered after cessation of exposure, soft or liquid faeces, alopecia, thin appearance, and/or decreased motor activity, no maternal death up to highest dose) Offspring: NOAEL: 70 mg Te/kg bw/d (HD: decreased foetal body weights, increased incidence of foetuses or litters with variations, malformations including hydrocephalus and with reversible delays in ossification, no individual numbers provided. It was stated that 'There were low incidences of hydrocephalus, enlarged and/or irregularly shaped anterior fontanelle, incomplete ossification of, or small holes in, the frontals and parietals; frontals with thickened ossification; umbilical hernia; fused pulmonary artery and aorta; asymmetric and/or irregularly shaped and/or fused sternebrae; and thickened areas in the ribs in foetuses of high-dosage pregnancies.'; No. (%) of foetuses with abnormalities: 3 (6.7); 6 (5.1); 4 (6.0); 2 (1.8); 11 (11.8) at 0, 0.7, 7, 70, 210 mg/kg bw/d, respectively); No. (%) of litters with abnormalities: 2 (22.2); 5 (33.3); 2 (25); 1 (7.1); 6 (46.2) at 0, 0.7, 7, 70, 210 mg/kg bw/d Te, respectively)	(Johnson *et al.*, 1988) also reported in (ECHA Dissemination, 2018)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Long Evans rats (5-11 dams per dose group and gestation day; 2-3 dams per control group and gestation day) K4	Tellurium (Purity: not provided) 13 mg Te/kg bw/d Single application on gestation days 7, 8, 9, 10, 11, 12, or 13 Vehicle: olive oil (suspension) Dams were allowed to deliver and offspring observed until PND 10; sacrifice on PND 10 and fixation of offspring in Bouin's solution, examination for hydrocephalus (increased ventricular dilatation was classified	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 13 mg Te/kg bw/d (hydrocephalus in offspring of animals treated on day 9 (14 of 75 (18.6%) offspring) or 10 (10 of 32 (31%) offspring); one offspring with hydrocephalus in the group treated on GD7 (1 of 33 (3%) offspring) and one in an offspring of the control group (1 of 94 (1.1%) offspring), but not in offspring of dams treated on any other day of gestation; no other malformations observed; Foetal resorptions were also observed, but examinations for uterine resorption sites were only	(Agnew and Curry, 1972) also reported in (ECHA Dissemination, 2018)

	as hydrocephalus) and other defects No information on maternal toxicity Application intramuscular	performed in animals which failed to deliver by GD 22 (2/10, 3/8, 0/11, 1/6, 1/7, 0/5, 1/5 dams treated on GD 7, 8, 9, 10, 11, 12, 13, respectively)	
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (32 dams per dose group, 16 dams in the control group) K4	Tellurium (Purity: not provided) 3300 ppm Te Application throughout gestation Dams (n=10) were allowed to deliver, foetuses were examined for hydrocephalus No information on maternal toxicity Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 165 mg Te/kg bw/d (Hydrocephalus were observed in 8/10 litters 4-5 days after birth, 47% (36/77) of all foetuses developed hydrocephalus, with up to 100% of all foetuses of a litter) Remark: No hydrocephalus was observed in preliminary experiments with two groups of four pregnant rats, which received 1250 or 2500 ppm Te.	(Agnew *et al.*, 1968)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Long Evans rats (> 100 dams, no further information) K4	Tellurium (Purity: not provided) 500, 1250, 2500 ppm Te (25, 62.5, 125 mg Te/kg bw/d) 'fed during pregnancy', dams of the high dose received normal diet 3-5 days before delivery Dams were allowed to deliver and offspring were examined for the occurrence of hydrocephalus Application via diet	Dams: NOAEL 125 mg Te/kg bw/d (no detailed information provided, but stated that they behaved normally, tolerated the diet well and delivered on schedule) Offspring: LOAEL 25 mg Te/kg bw/d (100% hydrocephalus in the highest dose group and 60-90% in the mid dose group, at the low dose group only a part of the litters were affected (60% according to Duckett, 1971); hydrocephalus detectable immediately after birth; new-borns appeared smaller than controls; all offspring died within the first month after birth; no detailed examination of the foetuses for other endpoints)	(Garro and Pentschew, 1964) also reported in (ECHA Dissemination, 2018)
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (30 dams in treatment group, 20 dams in control group) K4 (according to registration dossier	Tellurium (Purity: not provided) 3000 ppm Te (150 mg Te/kg bw/d) fed 'every day of gestation' Dams were allowed to deliver and offspring were examined for the occurrence of hydrocephalus Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 150 mg Te/kg bw/d (24 of the female rats fed tellurium gave birth to litters. 20 of the rats gave birth to litters in which all the animals were hydrocephalic, 4 gestating rats gave birth to normal offspring. The hydrocephalus was non-obstructive in type for the first few days, after which obstructions appeared. Most of the animals died by the end of the second week. Only 61 of the 207 hydrocephalic rats born alive were still alive at the age of 10 days and only 44	(Duckett, 1971) also reported in (ECHA Dissemination, 2018)

and the authors of this document)		survived until the age of 1 year.)	
Prenatal Developmental Toxicity Study Not according to guideline Deviations: not applicable GLP: no Female Wistar rats (20 dams in treatment group, 20 dams in test group) K4	Tellurium (Purity: not provided) 3000 ppm Te (180 mg/kg bw/d as calculated by the authors of the publication) fed 'every day of gestation' On GD 13 and 15 foetuses (number not specified) were removed via abdominal wall; after closing the wall the dams were allowed to deliver; Only foetuses of Te fed animals who eventually gave birth to hydrocephalic animals, and foetuses of similar age control rats, were examined. Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 180 mg Te/kg bw/d (morphological anomalies in the cells in the ependymal layer of the treated foetuses: plasmalemma was without microvilli and the number of mitochondria was 'greatly diminished'; mitochondria 'were often abnormal, smaller and darker than normal and showed distortion of cristae')	(Duckett, 1970) also reported in (ECHA Dissemination, 2018)
Developmental toxicity study No guideline followed Deviations: not applicable GLP: no data Female rats, strain not provided (20 animals/group) K4	Tellurium (Purity: not provided Diet with 2500 ppm Te (according to authors of the publication rats usually consumed 20 g of diet, i.e. 50 mg tellurium which corresponds to ca. 200 mg/kg bw/d) Group 1: Exposure during day 1-21 of gestation Group 2: exposure of 20 dams from GD 1 to 9 Group 3: exposure of 20 dams from GD 10 to 15 Group 4: exposure of 20 dams from GD 16 to 21 No information on maternal toxicity Application via diet	Dams: no NOAEL can be derived since effects on dams were not examined/reported Offspring: LOAEL 200 mg Te/kg bw/d Group 1: 12/20 dams gave birth to litters with about 8 pups, 6 out of 8 were hydrocephalic Group 2: no foetuses with hydrocephalus Group 3: 12/20 dams gave birth to hydrocephalic animals. Group 4: no foetuses with hydrocephalus Remark: In a second experiment 21 groups of 5 dams received single doses of 200 mg Te/kg bw/d via diet on different days during gestation. Three animals died and 71 gave birth to an average of 8 offspring. None of the offspring had a hydrocephalus. No further details of results provided	(Duckett *et al.*, 1971) also reported in (ECHA Dissemination, 2018)

K: Klimisch

In summary, there is consistent evidence from experimental studies with rats that tellurium

dioxide causes developmental toxicity after gestational exposure or exposure to weaning rats at doses which are not, or only slightly, toxic to dams. The most relevant effects caused by tellurium are severe malformations (i.e. hydrocephalus) and pup lethality. Supporting evidence comes from a series of studies with tellurium in rats and rabbits. Elementary tellurium caused hydrocephalus and other major malformations in the two species. Even single exposure to high doses during the relevant time period (GD 9 to 15) resulted in the formation of hydrocephalus.

The highest weight in the assessment is given to those studies which detected developmental toxicity and foetal and pup mortality without any maternal toxicity. These are the pre-natal developmental toxicity study in rats with dietary tellurium exposure (Garro & Pentschew, 1964), the pre-natal developmental toxicity study in rats with sub-cutaneous tellurium dioxide exposure (Perez-D'Gregorio & Miller, 1988) and reproductive screening study in rats with gavage exposure to tellurium dioxide (Anonymous, 2013c). The remaining studies can be regarded as supportive.

In conclusion, RAC concurs with the proposal of the DS that **classification for adverse effects on development of the offspring in Category 1B is justified**.

Adverse effects on or via lactation

No human data are available to assess effects via lactation. Data from experiments with tellurium dioxide are not available. One study in 2 lactating rats with tellurium exposure via diet containing 1.25% Te in comparison to 2 lactating controls was published. A daily dose of 625 mg/kg bw/d was derived, no information on purity of the test substance was provided. Only one dose group was used. A total of 40 offspring were studied, five tellurium exposed and five control pups were investigated at the indicated time points (PND 7, 14, 21, and 28) for toxic effects. Light and electron microscopy was performed in two pups from each group. It can be assumed that only until day 7 the tellurium exposure of the pups was only via milk. After that exposure to tellurium containing diet might also have occurred. No analysis of Te concentration in the milk was performed. The DS classified the study reliability as Klimisch 3.

No toxicity was reported in dams at the dose of 625 mg Te (equivalent to 782 mg tellurium dioxide/kg bw/d). In another dietary study, the prenatal developmental toxicity study in rats (Johnson, *et al.*, 1988), maternal toxicity was seen at doses ≥ 18 mg Te /kg bw/d.

Offspring showed clinical signs, grey coloured skin and the typical odour of garlic. By 2 weeks of age, all the tellurium exposed pups were lethargic compared to the controls, and showed evidence of hind limb paresis. The tellurium exposed pups gained weight more slowly than the control pups and appeared small for age, an effect that was strongest after 14 days of age. It is noted that in the second week of life, exposure via food cannot be excluded, but this is a time where a big contribution of the pup's food still comes from milk. Light and electron microscopy of nervous tissue from rat offspring exposed via lactation showed typical alterations, starting on day 7 of exposure, where exposure was solely via milk. These observations must be interpreted as induced by tellurium via milk.

In addition, the optic nerves were investigated, but demyelination was not evident before 14 days of age. However, at 7 days of age no myelination was present in either control or treated pups; therefore, it was not possible to detect any demyelination. Clear effects on the optic nerve were seen after 14 days.

It is acknowledged that the study has considerable limitations (low number of animals per group, no toxicity in dams, despite high exposure) but there is a clear causality between general exposure indication (greyish discolouration of the skin, garlic odour in dams and pups)

and histopathological changes in the pups, typical for tellurium intoxication starting on day 7 of exposure (sciatic nerves) and on day 14 of exposure (optic nerve). Further evidence for transfer of tellurium to milk comes from a study by Nishimura *et al.* (2003) who could demonstrate that 2% and 3.9% of ^{123m}Te after single i.v. administration to the dams were transferred to the pups on PND1 and PND7, respectively, which was demonstrated by the whole body retention method. On PND14 5% of the administered dose was detected in the pups.

Therefore, despite the deficiencies of the study, RAC concludes that **classification for 'Adverse effects on or via lactation' (Lact.; H362) is justified**.

10.11 Specific target organ toxicity-single exposure

Evaluation not performed for this substance.

10.12 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance.

10.13 Aspiration hazard

Evaluation not performed for this substance.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance.

12 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance.

13 ADDITIONAL LABELLING

Not applicable for this evaluation.

14 ANNEXES

Please see separate documents for non-confidential and confidential Annex I.

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Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

tellurium dioxide

EC Number: **231-193-1**

CAS Number: **7446-07-3**

Index Number: **052-RST-VW-Y**

Contact details for dossier submitter:

Version number: 03 **Date: 08 April 2019**

ANNEX 1 TO ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON TELLURIUM DIOXIDE

CONTENTS

ANNEX 1 TO ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON TELLURIUM DIOXIDE

ANNEX 1 TO ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON TELLURIUM DIOXIDE

1 PHYSICAL HAZARDS

1.1 Explosives

Evaluation not performed for this substance.

1.2 Flammable gases (including chemically unstable gases)

Evaluation not performed for this substance.

1.3 Oxidising gases

Evaluation not performed for this substance.

1.4 Gases under pressure

Evaluation not performed for this substance.

1.5 Flammable liquid

Evaluation not performed for this substance.

1.6 Flammable solids

Evaluation not performed for this substance.

1.7 Self-reactive substances

Evaluation not performed for this substance.

1.8 Pyrophoric liquids

Evaluation not performed for this substance.

1.9 Pyrophoric solid

Evaluation not performed for this substance.

1.10 Self-heating substances

Evaluation not performed for this substance.

1.11 Substances which in contact with water emit flammable gases

Evaluation not performed for this substance.

1.12 Oxidising liquids

Evaluation not performed for this substance.

1.13 Oxidising solids

Evaluation not performed for this substance.

1.14 Organic peroxides

Evaluation not performed for this substance.

1.15 Corrosive to metals

Evaluation not performed for this substance.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No relevant data available for this endpoint.

3 HEALTH HAZARDS

Acute toxicity

3.1 Acute toxicity - oral route

Evaluation not performed for this substance.

3.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

3.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

3.4 Skin corrosion/irritation

Evaluation not performed for this substance.

3.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

3.6 Respiratory sensitisation

Evaluation not performed for this substance.

3.7 Skin sensitisation

Evaluation not performed for this substance.

3.8 Germ cell mutagenicity

3.8.1 In vitro data

3.8.1.1 [Study 1]

Study reference:

Study report, 2012 [confidential]

Detailed study summary and results:

Test type

An in vitro bacterial reverse mutation assay according to OECD TG 471 was performed. GLP compliance is given (including certificate).

A reliability of 1 is given for this study in the registration dossier.

Test substance

- Test material used in the study is equivalent to the substance identified in the CLH dossier: tellurium dioxide
- Degree of purity: [confidential information]
- Impurities: no information available
- Test material form: particulate/ powder
- Batch number: [confidential information]

Administration/exposure

- Strains: S. typhimurium TA 1535, TA 1537, TA 98 and TA 100, and E. coli WP2 uvr A
- Type and composition of metabolic activation system:
  - species and cell type: rat liver, S9 mix
  - quantity: not provided
  - induced or not induced: induced
  - chemicals used for induction: phenobarbital/β-naphthoflavone
  - co-factors used: not provided
- Test concentrations, and reasoning for selection of doses: at least 5 analysable concentrations in all test strains in the main test should be present
  - Range finding test: 5000; 2500; 1000; 316; 100; 31.6 and 10 µg/plate (TA 98 and TA 100 with and without metabolic activation)
  - Initial Test: 5000; 1581; 500; 158.1; 50; 15.81; 5 and 1.581 µg test item/plate
  - Confirmatory Test: 1581; 500; 158.1, 50; 15.81; 5; 1.581 and 0.5 µg test item/plate
  - Complementary Confirmatory Test: 5.81 (probably typing error, it could be reasonably be assumed that the highest concentration tested was 15.81 µg/plate); 5; 1.581; 0.5; 0.1581; 0.05; 0.01581 and 0.005 µg test item/plate (TA1535; without metabolic activation)
  - Complementary Confirmatory Test: 5; 1.581; 0.5; 0.1581; 0.05; 0.01581; 0.005 and 0.001581 µg test item/plate (TA98, TA100 and TA1537 without metabolic activation)
- Method of application: plate incorporation method was used for the range finding and initial test and the pre-incubation method for the confirmatory and complementary tests
- Duration: preincubation period was 20 min and exposure duration was 48 hours.
- Number of replicates: 3
- Vehicle: methyl cellulose solution, 1 % (v/v), was used for preparing the stock solution and test formulations of powdered test item, used volume not given
- Statistical methods: no information available

Results and discussion

- Justification should be given for choice of tested dose levels: based on range-finding test (5000; 2500; 1000; 316; 100; 31.6 and 10 µg/plate), tested up to maximum concentration according to guideline
- Cytotoxic concentrations with and without metabolic activation:
    - observed in all tester strains with and without metabolic activation at the two or three highest concentrations of the initial mutation test,
    - stronger effects were seen in all tester strains with and without metabolic activation when the preincubation method (Confirmatory Mutation Test and Complementary Confirmatory Mutation Test) was used
- Genotoxic effects with and without metabolic activation: negative for all tested strains with and without metabolic activation
- Concurrent negative (solvent/vehicle) and positive control data:
    - negative control: yes, valid
    - solvent control: yes, valid
    - positive control: yes (9-aminoacridine, sodium azide, methylmethanesulfonate, 4-nitro-1,2-phenylenediamine (NPD), and 2-aminoanthracene), valid
- Indicate test-specific confounding factors such as pH, osmolarity, whether substance is volatile, water soluble, precipitated, etc., particularly if they affect the selection of test concentrations or interpretation of the results: no information available
- Statistical results: no statistical evaluation of results available, revertant colony numbers were not above the respective biological threshold, dose-related trends and treatment effects were not observed neither in the tests (Initial Mutation Test, Confirmatory Mutation Test and Complementary Confirmatory Mutation Test) nor in the test item treated groups
- Provide information that may be needed to adequately assess data for reliability
    - mean number of revertant colonies per plate and standard deviation: numerical values are not provided
    - mean numbers of revertant colonies were below the biological relevance when compared with solvent controls, within the historical control range and the normal biological variability of the test system for all treated groups
    - in each test viability of bacterial cells was confirmed by plating experiments
    - Evaluation criteria:
        - Validity given, if: in all strains of the main test the number of revertant colonies of controls (negative (vehicle/solvent) and positive controls) are in range of historical control data

- Positive response given, if: dose–related increase in the number of revertants occurred and/or; reproducible biologically relevant positive response for at least one of the dose groups occurred in at least one strain with or without metabolic activation.
- Biological relevant increase given, if: number of reversion was more than twice higher than reversion rate of vehicle control

3.8.1.2 [Study 2]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

An in vitro mammalian cell gene test according to OECD TG 476 was performed. GLP compliance is given (including certificate).

A reliability of 1 is given for this study in the registration dossier.

Test substance

- Test material used in the study is equivalent to the substance identified in the CLH dossier: tellurium dioxide
- Degree of purity: [confidential information]
- Impurities: no information available
- Test material form: particulate/ powder
- Batch number: [confidential information]

Administration/exposure

- Strain or cell type or cell line, target gene: mouse lymphoma L5178Y TK+/-3.7.2 C cells, at *tk* locus
- Type and composition of metabolic activation system:
  - species and cell type: rat liver, S9 mix
  - quantity: not provided
  - induced or not induced: induced
  - chemicals used for induction: phenobarbital/β-naphthoflavone
  - co-factors used: not provided
- Test concentrations, and reasoning for selection of doses if applicable:

  - Assay 1, 3-hour treatment with metabolic activation: 100; 75; 50; 25; 20; 15; 10; 7.5; 5; 2.5; 1.25 and 0.625 µg/mL
  - Assay 1, 3-hour treatment without metabolic activation: 80; 70; 60; 50; 40; 30; 20; 10; 5; 2.5; 1.25 and 0.625 µg/mL
  - Assay 2, 3-hour treatment with metabolic activation: 20; 17.5; 15; 12.5; 10; 7.5; 5; 2.5; 1.25 and 0.625 µg/mL
  - Assay 2, 24-hour treatment without metabolic activation: 15; 12.5; 10; 9; 8; 7; 6; 5; 4; 2; 1; 0.5 and 0.25 µg/mL
- Vehicle: methyl cellulose solution, 1 % (w/v), no further information available
- Method of application: in medium
- Duration: exposure duration was 3 and 24 hours, the expression time was 3 days, and selection time was two weeks
- Selection agent: 5-trifluorothymidine (TFT)
- Number of replication: duplicate cultures
- Determination of cytotoxicity: relative total growth
- Statistical methods: Dunnett's test for multiple comparison was performed for comparing log mutant frequency (LMF) of controls with LMF of each treatment dose. For testing the data for a linear trend in mutant frequency with treatment dose, a one-tailored, weighted regression test, which is not considering negative trends as significant, was used. In order to perform the statistical methods the calculation of the heterogeneity factor is required. The Microsoft Excel software was used for determining the statistical significance of mutant frequencies (total wells with clones).

Results and discussion

- Justification should be given for choice of tested dose levels: no information available
- Cytotoxic concentrations with and without metabolic activation:
  - Assay 1, 3-hour treatment with metabolic activation: no survival at 100, 75, 50, 25, and 20 µg/mL, marked cytotoxicity at 15 µg/mL (relative total growth of 4 %), evaluation of concentrations from 10 (relative total growth of 10 %) to 0.625 µg/mL
  - Assay 1, 3-hour treatment without metabolic activation: no survival at 80, 70, 60, 50, 40, and 30 µg/mL, evaluation of concentrations from 20 (relative total growth of 18 %) to 0.625 µg/mL
  - Assay 2, 3-hour treatment with metabolic activation: no survival at 20 µg/mL; marked cytotoxicity at 17.5; 15; 12.5; 10; 7.5 µg/mL, evaluation of concentrations from 5 (relative total growth of 12 %) to 0.625 µg/mL

  - Assay 2, 24-hour treatment without metabolic activation: no survival at 15 µg/mL; marked cytotoxicity at 12.5; 10; 9 µg/mL, evaluation of concentrations from 8 (relative total growth of 27 %) to 0.25 µg/mL
- Genotoxic effects with and without metabolic activation: negative with and without metabolic activation
- Concurrent negative (solvent/vehicle) and positive control data:
  - (true) negative control: no
  - solvent control: yes, valid
  - positive controls: yes (4-nitroquinoline-N-oxide and cyclophosphamide), valid
- test-specific confounding factors:
  - Effects of pH: no large changes
  - Effects of osmolality: no large changes
  - Water solubility: insoluble
  - Precipitation: For some concentrations, insolubility was detected in the final treatment medium at the end of the treatment.
- Statistical results
  - Assay 1, 3-hour treatment with metabolic activation: A statistical significant increase in mutation frequency was seen at 10, 7.5, 5, 2.5, and 1.25 µg/mL. However, the difference in mutation frequency of treated samples and corresponding vehicle controls did not exceed the global evaluation factor for 7.5, 5 and 2.5 µg/mL, thus the increases were regarded as not biological relevant. Sample concentrations of 10 and 1.25 µg/mL had a difference, which was higher than the global evaluation factor (values were over the limit of biological relevance) but a clear dose-response relationship was not seen and increases were not reproduced in Assay 2.
  - Assay 1, 3-hour treatment without metabolic activation: A statistical significant increase in mutation frequency was seen at 20 µg/mL. However, the difference in mutation frequency of treated samples and corresponding vehicle controls did not exceed the global evaluation factor, thus the increase was regarded as not biological relevant.
  - Assay 2, 3-hour treatment with metabolic activation: A statistical significant increase in mutation frequency was seen at 5 µg/mL. However, the difference in mutation frequency of treated samples and corresponding vehicle controls did not exceed the global evaluation factor, thus the increase was regarded as not biological relevant.
  - Assay 2, 24-hour treatment without metabolic activation: A statistical significant increase in mutation frequency was seen at 8 µg/mL. However, the difference in mutation frequency of treated samples and corresponding vehicle controls did not exceed the global evaluation factor, thus the increase was regarded as not biological relevant.
- Provide information that may be needed to adequately assess data for reliability

- frequency of mutations: numerical values are not provided
- evaluation criteria:
  - validity given, if: in negative (vehicle) controls mutant frequency in the cultures fall within the normal range (50-170 mutants per 10^6 viable cells) and plating efficiency is within the range of 65 to 120 % (end of expression period); positive controls induce a statistically significant increase in the mutant frequency; at least 4 concentrations are present, whereby the highest concentration leads to 80-90 % toxicity, engenders in precipitation or is 5 mg/mL, 5 µL/mL or 0.01 M or highest practical concentration.
  - Mutagenicity given, if: assay is valid; for one or more concentration statistically significant ($p<0.05$) and biologically relevant increases in mutation frequency are observed in treated cultures compared to the corresponding negative (vehicle) control values; reproducibility of increases in mutation frequency between replicate cultures and/or between tests (under same test conditions); linear trend analysis produces a significant ($p<0.05$) concentration-relationship; mutation frequency at concentration having the highest increase is at least 126 mutants per 10^6 viable cells (GEF = global evaluation factor) higher than the corresponding negative (vehicle) control values

3.8.1.3 [Study 3]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

An in vitro mammalian chromosome aberration test according to OECD TG 473 was performed. GLP compliance is given (including certificate).

A reliability of 1 is given for this study in the registration dossier.

Test substance

- Test material used in the study is equivalent to the substance identified in the CLH dossier: tellurium dioxide
- Degree of purity: [confidential information]
- Impurities: no information available
- Test material form: particulate/powder
- Batch number: [confidential information]

Administration/exposure

- Strain or cell type or cell line, target gene: Chinese hamster lung fibroblasts (V79)
- Type and composition of metabolic activation system:
  - species and cell type: rat liver, S9 mix
  - quantity: not provided
  - induced or not induced: induced
  - chemicals used for induction: phenobarbital/β-naphthoflavone
  - co-factors used: not provided
- Test concentrations, and reasoning for selection of doses:
  - Assay 1, 3-hour treatment without metabolic activation, harvest 20 hrs after beginning of treatment: 200; 100; 75; 50; 25; 12.5; 6.25, and 3.125 µg/mL
  - Assay 1, 3-hour treatment with metabolic activation, harvest 20 hrs after beginning of treatment: 200; 100; 75; 50; 25; 12.5; 6.25, and 3.125 µg/mL
  - Assay 2, 3-hour treatment without metabolic activation, harvest 28 hrs after beginning of treatment: 60; 40; 30; 20; 15; 10; 7.5, 5 and 2.5 µg/mL
  - Assay 2, 3-hour treatment with metabolic activation, harvest 28 hrs after beginning of treatment: 200; 100; 75; 50; 25; 12.5; 6.25, and 3.125 µg/mL
- Vehicle: methyl cellulose solution, 1 %, no further information available
- Method of application: in medium
- Duration: exposure duration was 3 and 20 hours, the fixation time was 20 and 28 hours
- Spindle inhibition: colchicine (0.2 µg/mL), stain: 5 % Giemsa solution
- Number of replications: duplicate cultures
- Number of cells evaluated: 100 metaphases from each culture
- Determination of cytotoxicity: as % relative survival compared to negative (solvent) control
- Other examinations:
  - Polyploidy: metaphases with approximate multiples of haploid chromosome number (n), other than the diploid number
  - Endoreplication: metaphases having chromosomes with 4, 8 and so on chromatids
- Statistical methods: Fisher's exact test was used for evaluating the number of cells with one or more chromosomal aberrations excluding gaps.

Results and discussion

- Justification should be given for choice of tested dose levels: no information available
- Cytotoxic concentrations with and without metabolic activation:

  - Assay 1, 3-hour treatment without metabolic activation, harvest 20 hrs after beginning of treatment: cytotoxicity at 200; 100, and 75 µg/mL (relative survival: 5, 30, and 45 %), evaluation of concentrations from 75 to 25 µg/mL
  - Assay 1, 3-hour treatment with metabolic activation, harvest 20 hrs after beginning of treatment: cytotoxicity at 200 and 100 µg/mL (relative survival: 11 and 30 %), evaluation of concentrations from 75 to 25 µg/mL
  - Assay 2, 3-hour treatment without metabolic activation, harvest 28 hrs after beginning of treatment: cytotoxicity at 60; 40; 30; 20; 15 and 10 µg/mL (relative survival: 5, 6, 3, 25, 43, and 38 %), evaluation of concentrations from 10 to 5 µg/mL
  - Assay 2, 3-hour treatment with metabolic activation, harvest 28 hrs after beginning of treatment: cytotoxicity at 200; 100, and 75 µg/mL (relative survival: 7, 19, and 37 %), evaluation of concentrations from 75 to 12.5 µg/mL
- Genotoxic with and without metabolic activation: negative, with and without metabolic activation
- Concurrent negative (solvent/vehicle) and positive control data:
  - negative control: yes, valid
  - solvent control: yes, valid
  - positive control: yes (cyclophosphamide and ethylmethanesulphonate), valid
- test-specific confounding factors:
  - Effects of pH: no large changes
  - Effects of osmolality: no large changes
  - Water solubility: water soluble
  - Precipitation:
    - Assay 1: at 200 and 100 µg/ml with and without metabolic activation a minimum of insolubility in final treatment medium was detected at the end of the treatment period
    - Assay 2: at 200 and 100 µg/ml with metabolic activation a minimum of insolubility in final treatment medium was detected at the end of the treatment period
- Statistical results: no statistically significant increase was observed after test item treatment
- Provide information that may be needed to adequately assess data for reliability
  - frequency of aberrations: is provided, but not increased
  - polyploidy: no information is provided in the registration dossier
  - number of cells with chromosome aberrations and type of chromosome aberrations given separately for each treated and control culture: no details were provided in registration dossier due to clear negative results in test item treated cells and clear positive results in controls
  - precipitation concentration: were observed equal or above 100 µg/mL

- mitotic index: relative survival (%) provided; at least 30 percent

Results are confidential for details see confidential annex. [confidential information]

3.8.1.4 [Study 4]

Study reference:

Study report, 2012 [confidential]

Detailed study summary and results:

Test type

An in vitro bacterial reverse mutation assay according to OECD TG 471 was performed. GLP compliance is given (including certificate).

A reliability of 1 is given for this study in the registration dossier.

Test substance

- Test material used in the study is not equivalent to the substance identified in the CLH dossier: tellurium was used instead of tellurium dioxide
- EC number: 236-813-4
- CAS number: 13494-80-9
- Degree of purity: [confidential information]
- Impurities: no information available
- Test material form: particulate/ powder
- Batch number: [confidential information]

Administration/exposure

- Strains: S. typhimurium TA 1535, TA 1537, TA 98 and TA 100, and E. coli WP2 uvr A
- Type and composition of metabolic activation system:
  - species and cell type: rat liver, S9 mix
  - quantity: not provided
  - induced or not induced: induced
  - chemicals used for induction: phenobarbital/β-naphthoflavone
  - co-factors used: not provided
- Test concentrations, and reasoning for selection of doses: at least 5 analysable concentrations in all test strains in the main test should be present

  - Range finding test: 5000; 2500; 1000; 316; 100; 31.6 and 10 µg/plate (TA 98 and TA 100 with and without metabolic activation)
  - Initial Test: 5000; 1581; 500; 158.1; 50; 15.81; and 5 µg test item/plate
  - Confirmatory Test: 5000, 1581; 500; 158.1, 50; 15.81; 5; and 1.581 µg test item/plate
  - Complementary Confirmatory Test: 158.1, 50, 15.81; 5; 1.581; 0.5; 0.1581; and 0.05 µg test item/plate
- Method of application: plate incorporation method was used for the range finding and initial test and the pre-incubation method for the confirmatory and complementary test
- Duration: pre-incubation period was 20 min and exposure duration was 48 hours.
- Number of replicates: 3
- Vehicle: methyl cellulose solution, 1 % (v/v), was used for preparing the stock solution and test formulations of powdered test item, used volume not given
- Statistical methods: no information available

Results and discussion

- Justification should be given for choice of tested dose levels: based on range-finding test (5000; 2500; 1000; 316; 100; 31.6 and 10 µg/plate), tested up to maximum concentration according to guideline
- Cytotoxic concentrations with and without metabolic activation:
  - at 5000 µg/plate in the Initial Mutation Test in strains TA98 and E. coli WP2 uvrA with metabolic activation were observed slight cytotoxic effects
  - a reduction in number of revertant colonies in comparison to vehicle control plates was observed in the Initial Mutation Test in strains TA100 at 5000 µg/plate without metabolic activation and in strains TA1535 and E. coli WP2 uvrA at 5000 µg/plate with metabolic activation
  - in the Confirmatory Mutation Test and Complementary Confirmatory Mutation Test in strains TA100, TA1535 and TA1537 (at 158.1 and 50 µg/plate) and E. coli WP2 uvrA (at 5000, 1581 and 500 µg/plate) without metabolic activation were observed stronger cytotoxic effects
- Genotoxic effects with and without metabolic activation: negative for all tested strains with and without metabolic activation
- Concurrent negative (solvent/vehicle) and positive control data:
  - negative controls: yes (no further information available), valid
  - solvent control: yes, valid
  - positive controls: yes, 9-aminoacridine, sodium azide, methylmethanesulfonate, 4-nitro-1,2-phenylenediamine (NPD), and 2-aminoanthracene, valid

- Indicate test-specific confounding factors such as pH, osmolarity, whether substance is volatile, water soluble, precipitated, etc., particularly if they affect the selection of test concentrations or interpretation of the results: no information available
- Statistical results: no statistical evaluation of results available, revertant colony numbers were not above the respective biological threshold, dose-related trends and treatment effects were not observed neither in the tests (Initial Mutation Test, Confirmatory Mutation Test and Complementary Confirmatory Mutation Test) nor in the test item treated groups
- Provide information that may be needed to adequately assess data for reliability
  - mean number of revertant colonies per plate and standard deviation: numerical values were not provided
  - mean numbers of revertant colonies were below the biological relevance when compared with solvent controls, within the historical control range and the normal biological variability of the test system for all treated groups
  - in each test viability of bacterial cells was confirmed by plating experiments
  - Evaluation criteria:
    - Validity given, if: in all strains of the main test the number of revertant colonies of controls (negative vehicle control, solvent control, and positive controls) are in range of historical control data, and in all test strains at were least five analysable concentrations present
    - Positive response given, if: dose–related increase in the number of revertants occurred and/or; reproducible biologically relevant positive response for at least one of the dose groups occurred in at least one strain with or without metabolic activation.
    - Biological relevant increase given, if: number of reversion was more than twice higher than reversion rate of vehicle control

3.8.2 Animal data

No data presented here.

3.8.3 Human data

No data presented here.

3.8.4 Other data

No data presented here.

3.9 Carcinogenicity

No relevant data available for this endpoint.

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 [Study 5]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

A reproduction/developmental toxicity screening test was performed according to OECD TG 421. GLP compliance is given (including certificate).

A reliability of 1 is given for this study in the registration dossier.

Test substance

- Test material used in the study is equivalent to the substance identified in the CLH dossier: tellurium dioxide
- Degree of purity: [confidential information]
- Impurities: no information available
- Test material form: particulate/powder
- Batch number: [confidential information]

Test animals

- Rat/Wistar/male and female
- No. of animals per sex per dose: 12 animals
- Age at the study initiation: approx. 10 weeks old at starting and 12 weeks at mating.
- weight at the study initiation: 331-371 g males and 195-247 g females

Administration/exposure

- Route of administration – oral (gavage)
- Duration and frequency of test/exposure period: males exposed for 28 days (14 days pre-mating and 14 days mating/post-mating); females exposed for 14 days pre-mating, up to 14 days mating period, through gestation, 4 days post-partum (day of birth, when parturition is completed, was defined as day 0 post-partum), and including the day before necropsy. The frequency was 7 days per week.
- Doses/concentration levels, rationale for dose level selection: maximum dose selected was 600 mg/kg bw/d, based on preliminary dose range-finding study
- Control group and treatment: yes, concurrent vehicle
- Historical control data: not provided in the dossier
- Vehicle: aqueous methyl cellulose, 1 %, 5 mL/kg bw, Lot/batch no.: O16147824 (Dow Chemicals)
- Test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation:
    - application volume was 5 mL/kg bw
    - analytical verification: performed three times (during first, midway, and last weeks of exposure period) for achieving concentration and homogeneity by a validated ICP method, test item formulations had actual concentrations of 95.2-105.3 % of the nominal concentrations, within the 100 ± 15 % acceptable range
- Actual doses (mg/kg bw/day) and conversion factor from diet/drinking water test: 0; 25; 120; and 600 mg/kg bw/d actual ingested

Description of test design:

- Details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy): M/F ratio 1:1 per cage, for mating period (14 d) or until copulation occurred, vaginal smear were examined daily and presence of vaginal plug or sperm was regarded as evidence of copulation (defined as day 0 of pregnancy), sperm positive females were caged individually
- Premating exposure period for males and females (P): 14 days
- Standardization of litters: no
- Parameters assessed for P:
    - cage side observations: twice daily
    - clinical observations: general clinical observations (pertinent behavioural changes, signs of difficult or prolonged parturition and all signs of toxicity including mortality) were checked once a day; detailed clinical observations (skin, fur, eyes, mucous membranes, occurrence of secretions and excretions, and autonomic activity, changes in gait, posture, response to handling, presence of clonic or tonic movements, tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma, stereotypies, difficult or prolonged parturition or bizarre behaviour

(e.g. self-mutilation, walking backwards)) were checked once before first exposure and thereafter once a week

- body weight: all parental animals on day 0, afterwards weekly, and at termination; females GD 0, 7, 14, and 20 and postpartum PPD0 (24 h after parturition) and 4, additionally on GD 4, 10, and 17 for adjusting treatment volumes
- food consumption and compound intake: yes, re-weighing of non-consumed diet on day 7 and afterwards weekly
- water consumption and compound intake: no
- other: GD13 sperm positive females were examined for vaginal bleeding or placental signs
- oestrous cycle length and pattern: ovaries (including follicular, luteal, and interstitial compartments), epithelial capsule and ovarian stroma were detailed histologically examined
- sperm examination: stages of spermatogenesis in the male gonads were evaluated and histopathology of interstitial testicular cell structure was performed
- all observations were reported individually
- sacrifice: all surviving males were sacrificed after 28 days; all surviving females were sacrificed after 4 days post-partum, females (not-mated, not delivered) were sacrificed 26 days after last day of mating
- gross necrospcopy: performed on all animals, cranium, thoracic and abdominal cavities were opened and appearance of tissues and organs was observed macroscopically, if abnormalities were detected details of the location, colour, shape and size were recorded
- histopathology/organ weights: histological examination was performed of brain, uterus, ovaries, vagina, testes, epididymides, prostate, seminal vesicles with coagulating glands, pituitary, number of implantation sites and of corpora lutea in controls and animals exposed to high dose, animals found dead or observed abnormalities; organ weights were determined in uterus (with and without cervix), vagina, testes, epididymides, prostate, seminal vesicles with coagulating glands, brain, ovaries, pituitary, and of paired organs (absolute and relative (to body and brain weight) organ weights)

- Reproductive indices:
  - Male/female mating and fertility index and gestation index for females

- Parameters assessed for F1:
  - number and sex of pups, stillbirths, live births, runts (significantly smaller than normal pups) and presence of gross abnormalities for each litter were assessed after delivery
  - litters checked daily for number of alive and dead pups, dead pups were included in macroscopic examinations and abnormalities reported
  - number, sex and weight (PPD 0/1 and 4) of live pups was determined
  - dead, cannibalised pups were not examined macroscopically, but sex determined if possible

  - observations were reported individually
  - Sacrifice/ gross necropsy: sacrificed at PND 4 and externally examined for abnormalities
- Offspring viability indices:
  - Survival and sex ratio index
  - Pre-implantation, intrauterine, and total mortality index

Results and discussion

- Actual dose received: 0; 25; 120; and 600 mg/kg bw/d (actual ingested)
- Statistical treatment of results: For testing homogeneity of variances between groups, Bartlett's homogeneity of variance test was used. If no significant heterogeneity was detected, a one-way ANOVA was performed. For a significant result, the significance of intergroup differences was assessed by Duncan Multiple Range test. If Bartlett's test was significant, Kruskal-Wallis test and Mann-Whitney U-test were used for analysis of variances and inter-group comparisons. In addition, the Chi-squared test was used, if appropriate. For statistical evaluation the statistical programme SPSS PC+4.0 was used.

For P:

- Mortality
  - 600 mg/kg bw/d: one deceased female without successful coitus was found on day 13 of the mating period; 5 female animals died between days 14 and 45; one female animal deceased on day 27, but proved to be a gavage accident at necropsy
- Clinical signs:
  - 120 and 600 mg/kg bw/d groups: dark faeces in all males and pregnant females
  - 120 mg/kg bw/d group: limited use of hind-limbs in one male animal
  - 600 mg/kg bw/d group: decreased activity, dark faeces, hunched back, and piloerection were seen in all treated females and additionally salivation, lethargy, red liquid from vulva were seen in surviving non-pregnant females
  - Treatment-related clinical signs in deceased animals: decreased activity, dark, liquid faeces, hunched back, laboured respiration, lethargy, piloerection and red liquid from mouth and vulva
  - Incidental findings (not treatment-related): missing right testes, broken left incisor, and missing fur in the chin area
  - control and 25 mg/kg bw/d groups: no clinical signs observed
- Body weight and food consumption:
  - 120 and 600 mg/kg bw/d: reduced body weight or body weight gain in both sexes; terminal body weights in males were about 7 and 14 % lower than controls; body weights on day 14

in females were about 5 and 11 % lower than controls, respectively (during pregnancy the effect was more pronounced), and at termination body weight in females were about 18 and 30 % below controls, respectively

  - 25 mg/kg bw/d: no treatment-related effects
  - food consumption: reduction in line with body weight effects
- Mating procedure:
  - 600 mg/kg bw/d: duration of mating period was significantly affected; for 2 females no successful coitus was observed during 14 d mating period (usually successful coitus occurred within 5 days) and one deceased female without successful coitus was found on day 13 of mating period
- Oestrous cycle:
  - 600 mg/kg bw/d: mainly diestrus phases characterised the oestrous cycle of animals
- Sperm examination:
  - no difference between highest dose group and controls for male gonads, testicular interstitial cell structure, spermatogenic cells (development and differentiation), and microscopic changes in reproductive organs
  - 600 mg/kg bw/d: unilateral distribution of testicular observation, not treatment-related
- Reproductive indices:
  - 600 mg/kg bw/d: mating indices reduced with 73 %, compared to 100 % in control, low and mid dose groups
  - 600 mg/kg bw/d: fertility indices reduced with 63 % (3/11 non-pregnant females), compared to 100 % in control, low and mid dose groups
  - 600 mg/kg bw/d: gestation index reduced with 0 %, compared to 92 % in control (one animal with stillborns, considered as incidental), 100 % in low and 67 % in mid (2/12 animals with stillborns) dose groups
- Organ weights:
  - Males: weights of seminal vesicles as absolute and relative weights (adjusted to brain weight) were statistically significant decreased ($p<0.05$) at 600 mg/kg bw/d compared to controls, no histological evidence for effects on male reproductive system was seen, further statistical differences in organ weights were assigned to body weight differences
  - Females: mean absolute weight of vagina was statistically significantly decreased ($p<0.01$) at 600 mg/kg bw/d compared to controls (47 % below controls), probably related to ovary atrophy due to sensitivity of vagina weight to altered ovarian hormone production, further statistical differences in relative organ weights were observed, but assigned to body weight differences (see section on body weight)
- Gross pathology

  - 600 mg/kg bw/d in 6 deceased females: treatment-related macroscopic changes including black/grey discoloration/focus of the adrenal gland, brain, stomach, small intestines, caecum, colon, rectum, thymus, kidney, mesenteric lymph node and uterus, in 2/6 females pale discoloration of liver, 1/6 females a small thymus (treatment-related)
  - 600 mg/kg bw/d: 4/6 females were non-pregnant (decreased or no corpora lutea and and implantation sites at necroscopy), 4/6 had small thymuses
  - 120 and 600 mg/kg bw/d: treatment-related macroscopic findings were observed, 2/12 and 1/6 had pale colouration of the liver, respectively
  - discoloured (black/grey) organs included adrenal gland, brain, stomach, small intestines, caecum, colon, rectum, thymus, kidney, mesenteric lymph node, testis, ovary and/or uterus
- Histopathology of deceased animals
  - Histopathological examination of one deceased female was not possible due to cannibalisation of internal organs
  - 5 deceased animals: treatment-related effects seen in ovary, uterus, vagina, liver, kidney, thymus, mesenteric lymph node, stomach and caecum,
  - 3/5: atrophy (minimal to moderate) of ovary, uterus, and/or vagina, minimal/moderate accumulation of pigmented macrophages in the medulla of mesenteric lymph node
  - 2/5: moderate hepatocellular necrosis and/or mild moderate diffuse vacuolation
  - 1/5: moderate vacuolation of corpora lutea in right ovary, mild blue/black diffuse pigment deposits of right ovary, mild bilateral necrosis of cortical tubules in the kidney associated with mild mixed cellular peritubular/perivascular infiltrate and moderate lymphoid atrophy of the thymus, mild mucosal erosion of the glandular stomach, mild granular/crystalline foreign material in the lumen of caecum
  - Other findings were incidental or agonal in nature and thus not treatment-related
- Histopathology of animals from scheduled necropsy
  - 600 mg/kg bw/d: treatment-related findings such as atrophy in ovary, vagina, uterus, and/or thymus, hepatocellular vacuolation or necrosis in liver, and accumulation of pigmented macrophages in mesenteric lymph node were observed
  - Ovary: occasionally blue/black diffuse pigment deposits, reduced number/size of follicles/corpora lutea
  - Uterus: low columnar luminal and glandular epithelium, reduced endometrium/myometrium
  - Vagina: attenuated epithelium comprising 2-3 cell layers
  - Thymus: lymphoid atrophy and decreasing number of lymphocytes resulting in decreased cell density, decreased compartment size (more pronounced in cortex), corresponding to organ weight change related to brain weight, various degree of pigmented macrophages in the medulla of mesenteric lymph nodes

  - Liver: vacuolation of hepatocytes containing predominantly large well-defined round vacuoles with displaced nuclei to the periphery, necrotic processes of the liver are characterised by lysis of nuclei and increased eosinophilia of cytoplasm
  - severity and incidence of treatment-related microscopic effects were dose-dependent
  - 120 mg/kg bw/d in females: only liver was affected
  - 120 and 600 mg/kg bw/d in males: dose-related accumulation of pigmented macrophages in mesenteric lymph nodes was observed and confirmed at necropsy
- Effect levels (given in dissemination database[1]):
  - NOAEL (male): 600 mg/kg bw/d, based on no effects on male reproductive system
  - NOAEL (female): 25 mg/kg bw/d, based on effects on female reproductive system at 120 and 600 mg/kg bw/d
  - NOAEL (male/female): 25 mg/kg bw/d, based on systemic effects in parental animals

For F1 and litters:

- Viability (offspring)
  - 600 mg/kg bw/d: no live pups, 16 pups were deceased, negative in floating tests, and were not nursed, 3 pups were cannibalised on day 0
  - 120 mg/kg bw/d: 33/137 stillborn pups, 28/137 pups were born alive but died shortly after (positive in floating test), 39 cannibalised pups, and 65 were not nursed, more male than female pups died between PND0-PND4
  - 25 mg/kg bw/d: no effect on number of live born pups (148/173), 33 pups did not suckled, in each case one pup was pale and one was cold and cyanotic, on PND4 the survival index was 75 % and therefore in the lower area of the normal control range
- Clinical signs: not examined
- Body weight:
  - PND0: adverse effects on offspring body weight were observed in all treated animals (all doses),
  - PND0: mean litter weights, pups body weight for all pups or per litter were lower in F1 generation in comparison to controls, mean body weight for all pups was statistical significant ($p<0.05$ or $p<0.01$)
  - PND4: pup body weight and body weight gain of low and mid dose were similar to controls
  - Total litter weights were lower than the normal control range at 120 mg/kg bw/d on PND0 and 4 and at 120 mg/kg bw/d at PND0, observed differences were assigned to pup mortality rather than weight of surviving pups being affected

[1] ECHA Dissemination: Information on Chemicals - Registered Substances. European Chemicals Agency. Online: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances 2018 (tellurium: last modified 25 May 2018; tellurium dioxide: last modified 15 January 2018)

- Sexual maturation: not examined
- Organ weights: not examined
- Gross pathology:
    - 600 mg/kg bw/d: in two litters treatment-related findings were observed in the cranium region (absence of cranial region of the head with reduced brain size, but covered by skin was noted in 4 deceased pups) and skin/subcutis (16 deceased pups had subcutaneous gelatinous material on the whole body)
- Histopathology: not examined
- Effect levels (given in dissemination database):
    - LOAEL (male/female): 25 mg/kg bw/d, based on pup mortality

3.10.1.2 [Study 6]

Study reference:

Johnson, E. M., Developmental Toxicology Investigation of Tellurium, Fundamental and Applied Toxicology, 11, 691-702, 1988

Detailed study summary and results:

Test type

In a prenatal developmental toxicity study (similar to OECD TG 414), pregnant rats were exposed to 0, 30, 300, 3000 or 15,000 ppm tellurium by diet from day 6 through 15 of gestation and effects on fertility and sexual function of female rats and malformations (external, visceral, or skeletal) and variations of foetuses were evaluated. GLP compliance is given according to "Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (U.S. FDA, 1978)".

Test substance

- Test material used in the study is not equivalent to the substance identified in the CLH dossier: tellurium was used instead of tellurium dioxide
- EC number: 236-813-4
- CAS number: 13494-80-9
- Degree of purity: 99.99 %
- Test material form: lumps, for study a powder with a nominal particle diameter less than 40 µm was produced
- Impurities: no information available
- Batch number: no information available

Test animals

- Rats/Sprague-Dawley (Crl COBS CD (SD) BR)/females
- No. of animals per sex per dose: 32 or 33 pregnant females
- Age and weight at the study initiation: young adults, 209 to 337 g

Administration/exposure

- Route of administration – oral (feed)
- duration and frequency of test/exposure period: only females, days 6 through 15 of gestation
- doses/concentration levels: 0, 30, 300, 3000 or 15,000 ppm tellurium
- rationale for dose level selection: dose ranging finding studies
- control group and treatment: yes, treated analogously as treatment groups
- historical control data: not provided in the dossier
- vehicle: diet (Ralston Purina Certified Laboratory Animal Meal 5002) contained adequate quantities of test substance to ensure administered doses from day 6 to 15 of gestation
- test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation: feed and pulverised tellurium were mixed in a drum tumbler to produce needed concentrations, rats were fed with the powder of feed and test substance
- actual doses (based on quantity of feed consumption): 0, 2.2, 19.6, 165.6 and 633.4 mg/kg bw/day from days 6 through 10 and 0, 1.9, 18.0, 173.0, and 579.4 mg/kg bw/day for days 11 through 15 of gestation
- analytical verification of doses: prior to use prepared concentrations of feed and test substance mixtures were weight and analysed, content of tellurium in feed was within 2.7 % of target value
- housing: individually, wire-bottom cages, temperature 72 ± 2 F, relative humidity 55 ± 10 % and photoperiod (hrs dark / hrs light): 12/12

Description of test design:

- Details on mating procedure: females were mated with males (no further information available), microscopically observed sperm in vaginal smear was regarded as day 0 of gestation
- Premating exposure period for males and females (P and F1): none
- Groups of 32/33 presumed pregnant females were randomly (computer-generated random-number sequence adjusted for body weight at day 0) assigned to 4 treatment groups
- Standardization of litters: no
- Parameters assessed for P:
    - cage side observations: yes, twice daily
    - detailed clinical observations: yes, daily

  - body weight: yes, seven to nine times during acclimation period, GD 0, daily during dosage and post-dosage
  - food consumption and compound intake: yes, recorded for days 0-5, 6-10, 11-16 and 17-20
  - post-mortem examinations: yes
  - GD 20: 2/3 of the females underwent caesarean section, 1/2 of the foetuses were examined for soft tissue anomalies and 1/2 for osseous skeletal status; 1/3 of the dams delivered naturally; foetuses and dams were sacrificed on PND 7
  - sacrifice on PND 7
  - ovaries and uterine examinations: yes, number of corpora lutea, number of implantations, number of foetuses, number of early/late resorptions

- Parameters assessed for F1:
  - body weight: yes
  - sex: yes
  - external examinations: all per litter
  - soft tissue and skeletal examinations: half per litter
  - head examinations: yes, for stillborn, found dead or killed at PND 7 pups
- Post exposure observation period: until PND 7

Results and discussion

- Actual dose received by dose level (based on quantity of feed consumption): 0, 2.2, 19.6, 165.6 and 633.4 mg/kg bw/day from days 6 through 10 and 0, 1.9, 18.0, 173.0, and 579.4 mg/kg bw/day for days 11 through 15 of gestation
- Statistical treatment of results: The differences in the data were considered statistically significant at probability of $p<0.05$ and $p<0.01$. The Bartlett's test of homogeneity of variances followed by Dunnett's test was used for analysing maternal body weight data, foetal body weights, anomaly averages, and ossification site data. Maternal physical sign data, proportion data from foetal evaluations, and proportion data for pups and litters were analysed using the variance test for homogeneity of binomial distribution. The Bartlett's test of homogeneity of variances followed by Dunn's method of multiple comparisons (if statistical significant) or if analysis of variances was not appropriate the Kruskal-Wallis test was applied for evaluating the maternal and pup body weights during the lactation period and average litter sizes. For analysing the data of number of implantations, incidence of foetal resorption, and number of live and dead foetuses at caesarean section the Kruskal-Wallis test followed by Dunn's method of multiple comparisons (if statistical significant) were applied.

For P:

- Mortality: no mortalities were observed
- Clinical Signs:
    - thinner appearance at 3,000 and 15,000 ppm (significantly increased)
    - at 15,000 ppm pre-parturitional vaginal bleeding was significantly increased
    - decreased motor activity
- Body weight and food consumption: at 300, 3,000, and 15,000 ppm body weight gain and food consumption were significantly decreased - in a concentration-dependent manner - during gestation (see **Error! Reference source not found.**)
- Gross pathology:
    - One rat of the high dose group had a mottled liver at GD 20
- Oestrous cycle: not affected,
- Histopathology:
    - No effects on the incidence of pregnancy, average numbers of corpora lutea, implantations, and resorptions for caesarean-delivered foetuses at GD 20 (see **Error! Reference source not found.**)
    -
- Effect levels (given in dissemination database):
    - NOAEL: 30 ppm (diet) based on maternal toxicity

For F1 and litters:

Caesarean-delivered foetuses (see **Error! Reference source not found.**):

- Viability: average number of live and dead foetuses or litter size is not affected by test substance
- Body weight: foetuses (male/female) in the two highest dose groups were treatment-related affected; dose-dependent decrease in males at 3,000 and 15,000 ppm (significant)
- Sex ratio: not affected
- Variations/malformations:
    - increased incidences of variations (litters and foetuses), malformations (foetuses), and delayed ossifications (foetuses)
    - most common malformation: internal hydrocephalus with slight to marked dilation of the lateral ventricles (slight to marked dilation of third and/or fourth ventricles in more severely affected foetuses)
    - at 3,000 and 15,000 ppm: moderate dilation of renal pelvis observed
    - at 15,000 ppm: two foetuses had a hydrocephalus, one of the two had an enlarged fontanelle bordered by haemorrhagic area

- at 15,000 ppm: other malformations included kinked and /or stubbed tails, rotation of a hind limb or foot, a malformed retina, mal-positioned manubrium and clavicles, short radius, ulna and/or femur, wavy ribs, and a thickened or split rib
- of previous affected foetuses many also had delayed ossifications: parietals, interparietals, supraossipitals, vertebral and sternal centra, pubes, ischia, and/or ribs

Naturally delivered pups (see **Error! Reference source not found.**):

- viability:
  - in each dose groups were stillbirths observed, not dose-dependent and also present in controls
  - at 15,000 ppm: statistical significant decrease in pup viability during period until PND7, smaller litter sizes and decreased pup survival in comparison to controls
- body weight: slightly decreased (not significantly) in 3,000 and 15,000 ppm dose group compared to controls at PND7
- malformations/ variations:
  - no anomalies (gross, external or visceral) observed in pups sacrificed on PND7
  - at 15,000 ppm: slight to extreme incidences of dilation of the lateral ventricles in pups
- Effect levels (given in dissemination database):
  - NOAEL: 300 ppm/18 mg/kg bw/d (diet) based on developmental toxicity

Table 1: Effects of tellurium exposure on mortality, body weight, and feed intake of pregnant rats.

Parameters	0 ppm	30 ppm	300 ppm	3,000 ppm	15,000 ppm
Mortality/pregnant/ number of treated females	0/22/22	0/20/22	0/22/22	0/21/22	0/20/22
No. pregnant at Day 20, Caesarean section	22	20	21 [a]	21	20
Maternal body weight (g)					
Day 0 av bw (mean ± SD)	272.9 ± 18.8	283.1 ± 23.5	272.7 ± 22.8	268.0 ± 25.0	273.2 ± 24.0
Day 6 av bw (mean ± SD)	300.5 ± 18.8	310.0 ± 25.3	299.9 ± 22.5	295.6 ± 23.5	296.9 ± 23.9
Day 20 av bw (mean ± SD)	398.8 ± 20.0	408.1 ± 30.2	390.8 ± 23.9	379.5 ± 23.9	245.3 ± 31.6 [b]
Maternal body weight change (g)					
Days 6-9 av	+8.7	+10.7	+4.9*	-4.5**	-17.4**
Days 6-15 av	+36.7	+36.3	+26.8**	+16.1**	-30.4**
Days 15-20 av	+61.6	+61.3	+64.1	+67.9	+78.8
Feed intake (g)					
Days 6-10 av	113.4	115.2	99.7**	81.0**	60.2**
Days 11-15 av	111.2	109.3	96.9*	88.5**	53.4**

* Significantly different from control group (p≤0.05). **Significantly different from control group (p≤0.01). [a]: One pregnant female excluded (inadvertently sacrificed on day 19 of gestation). [b]: no significance was indicated for this effect, unclear if this is a spelling mistake. Results taken from Johnson et al. (1988).

Table 2: Effects of tellurium exposure on *in utero* development of rats.

Parameters	**0 ppm**	**30 ppm**	**300 ppm**	**3,000 ppm**	**15,000 ppm**
Mean No. corpora lutea (mean ± SD)	15.6 ± 2.0	15.2 ± 2.8	15.6 ± 1.9[a]	16.0 ± 2.7	16.0 ± 2.2
Mean No. implant-tations (mean ± SD)	14.2 ± 2.1	13.6 ± 3.8	14.5 ± 1.7	14.6 ± 2.2	14.2 ± 1.6
Mean No. resorptions (mean ± SD)	1.0 ± 1.0	1.4 ± 1.1	1.1 ± 1.2	1.5 ± 1.6	1.4 ± 1.6
Mean No. litter size (mean ± SD)	13.2 ± 1.7	12.2 ± 3.6	13.4 ± 1.9	13.1 ± 2.1	12.8 ± 2.0
No. of live/dead foetuses	291/0	244/0	281/0	275/0	255/1
% males	52.8	48.7	45.9	50.6	48.8
Mean weight (g)					
Male foetuses (mean ± SD)	3.42 ± 0.29	3.48 ± 0.28	3.43 ± 0.27	3.37 ± 0.26	3.08 ± 0.51*
Female foetuses (mean ± SD)	3.24 ± 0.25	3.30 ± 0.23	3.25 ± 0.26	3.21 ± 0.28	2.90 ± 0.50*
% litters/foetuses with variations	18.2/2.1	35.0/2.9	28.6/3.2	57.1*/10.6	100**/40.6
No. (%) litters with dilated lateral ventricles	1(4.6)	0	1(4.8)	3(14.3)	17(85.0)*
No. (%) foetuses with dilated lateral ventricles	1(0.7)	0	1(0.7)	11(8.3)	67(54.9)*
(%) foetuses/litters with slight dilation	4.6/0.7	0/0	4.8/0.7	14.3/6.8	60/23.8
(%) foetuses/litters with moderate dilation	0	0	0	4.8/1.5	40/24.6

* Significantly different from control group (p≤0.05). **Significantly different from control group (p≤0.01). a: One pregnant female excluded (inadvertently sacrificed on day 19 of gestation). Results taken from Johnson et al. (1988).

Table 3: Effects of tellurium exposure on foetuses of rats.

Parameters	**0 ppm**	**30 ppm**	**300 ppm**	**3,000 ppm**	**15,000 ppm**
No. rats treated	10	9	10	11	10
No. (%) with litters	10(100)	9(100)	10(100)	11(100)	10(100)
Gestation duration (days, mean ± SD)	23.1 ± 0.6	23.2 ± 0.4	23.0 ± 0.0	23.2 ± 0.4	23.6 ± 0.7
litter size (live and dead, mean ± SD)	13.7 ± 1.2	14.1 ± 1.5	12.8 ± 1.6	14.3 ± 2.3	11.6 ± 3.4
No. (%) dams with stillborn	0	1(11.1)	2(20.0)	4(36.4)	3(30.0)
No. live pups delivered	137	127	128	157	116
No. (%) surviving 7 days	130(94.9)	120(95.2)	121(96.0)	145(96.0)	88(77.7)**
Pup weight (Day 7, mean ± SD)	11.6 ± 1.6	12.5 ± 1.4	11.5 ± 1.3	10.8 ± 1.6	10.7 ± 1.4
% pups/litters with dilated lateral ventricles day 7	0/0	0.8/11.1	0/0	0/0	60.9**/75.0**

* Significantly different from control group (p≤0.05). **Significantly different from control group (p≤0.01). Results taken from Johnson et al. (1988).

3.10.1.3 [Study 7]

Study reference:

Johnson, E. M., Developmental Toxicology Investigation of Tellurium, Fundamental and Applied Toxicology, 11, 691-702, 1988

Detailed study summary and results:

Test type

In a prenatal developmental toxicity study (similar to OECD TG 414), pregnant rabbits were exposed to 0, 17.5, 175, 1,750 or 5,250 ppm tellurium by diet from day 6 through 18 of gestation and effects on fertility and sexual function of female rabbits and malformations (external, visceral, or skeletal) and variations of foetuses were evaluated. GLP compliance is given according to "Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (U.S. FDA, 1978)".

A reliability of 2 is given for this study in the registration dossier.

Test substance

- Test material used in the study is not equivalent to the substance identified in the CLH dossier: tellurium was used instead of tellurium dioxide
- EC number: 236-813-4
- CAS number: 13494-80-9
- Degree of purity: 99.99 %
- Test material form: lumps, for study a powder with a nominal particle diameter less than 40 µm was produced
- Impurities: no information available
- Batch number: no information available

Test animals

- Rabbit/White New Zealand/male and female
- No. of animals per sex per dose: 17 females
- Age and weight at the study initiation: 5.5 months (17 days for acclimation), between 2.81 and 4.44 kg

Administration/exposure

- Route of administration – oral (feed)

- duration and frequency of test/exposure period: only females, days 6 through 18 of gestation
- doses/concentration levels: 0, 17.5, 175, 1,750 or 5,250 ppm tellurium
- rationale for dose level selection: based on dose ranging finding studies conducted in rats
- control group and treatment: yes, treated analogously as treatment groups
- historical control data: not provided in the dossier
- vehicle: diet (Ralston Purina Certified Laboratory Chow 5322) contained adequate quantities of test substance to ensure administered doses from day 6 to 18 of gestation
- test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation: for feeding rabbits a California Master pellet mill was used for preparing pellets of feed and pulverised tellurium (containing appropriate concentrations of test substance)
- actual doses: no information available
- analytical verification of doses: prior to use prepared concentrations of feed and test substance mixtures were weight and analysed, content of tellurium in feed was within 2.7 % of target value
- housing: individually, wire-bottom cages, temperature 68 ± 4 F, relative humidity 50 ± 15 % and photoperiod (hrs dark / hrs light): 12/12

Description of test design:

- Details on mating procedure: intravenous administration of 20 USP units/kg of human chorionic gonadotropin to females 3 hours prior to artificial insemination; females were artificially inseminated with approx. 0.25 mL semen (approx. 6.0 x 10^6 spermatozoa) from 5 different proven male breeders (same strain and source as female animals), day of artificial insemination was regarded as day 0 of gestation
- Premating exposure period for males and females (P and F1): none
- Groups of 17 presumed pregnant females were randomly (computer-generated random-number sequence adjusted for body weight at day 0) assigned to 4 treatment or a control group
- standardization of litters: no
- Parameters assessed for P:
    - cage side observations: yes, twice daily
    - detailed clinical observations: yes, daily
    - body weight: yes, weekly during acclimation period, GD 0, daily afterwards until sacrifice
    - Food consumption and compound intake: yes, recorded daily during study period. Determination of feed intake was done by differential weighing of diet jars. By dividing, the observed food consumption for the designated period through the average body weight during this period was performed for calculating the individual milligrams per kilogram per day dosages consumed.
    - post-mortem examinations: yes

  - GD 29: all surviving does were sacrificed, 1/2 of the foetuses were examined for soft tissue anomalies and 1/2 for osseous skeletal status; 1/3 of the dams delivered naturally; foetuses and dams were sacrificed on PND 7
  - sacrifice on day 29 of gestation
  - ovaries and uterine examinations: yes, number of corpora lutea, number of implantations, number of foetuses, number of early/late resorptions

- Parameters assessed for F1:
  - viability
  - body weight: yes
  - sex: yes
  - external examinations: yes, all per litter
  - soft tissue and skeletal examinations: yes, all per litter
  - head examinations: yes, all per litter
- Post exposure observation period: no

Results and discussion

- Statistical treatment of results: The differences in the data were considered statistically significant at probability of $p<0.05$ and $p<0.01$. The Bartlett's test of homogeneity of variances followed by Dunnett's test was used for analysing maternal body weight data, foetal body weights, anomaly averages, and ossification site data. Maternal physical sign data, proportion data from foetal evaluations, and proportion data for pups and litters were analysed using the variance test for homogeneity of binomial distribution. The Bartlett's test of homogeneity of variances followed by Dunn's method of multiple comparisons (if statistical significant) or if analysis of variances was not appropriate the Kruskal-Wallis test was applied for evaluating the average litter sizes. For analysing the data of number of implantations, incidence of foetal resorption, and number of live and dead foetuses at caesarean section the Kruskal-Wallis test followed by Dunn's method of multiple comparisons (if statistical significant) were applied.

For P (see **Error! Reference source not found.**):

- Mortality: no mortalities were observed
- Clinical signs:
  - at 1,750 and 5,250 ppm: statistically significant ($p<0.05$) toxicity was observed (thin appearance, alopecia, soft and liquid feces, and/or decreased motor activity)
  - at 5,250 ppm: statistically significant ($p<0.05$) in treatment-related adverse clinical signs

- Body weight and food consumption: at 1,750, and 5,250 ppm body weight gain and food consumption were significantly decreased - in a concentration-dependent manner - during gestation.
- Gross pathology: not affected
- Oestrous cycle: not affected
- Histopathology:
    - No effects on the incidence of pregnancy, average numbers of corpora lutea, implantations, resorptions, litter sizes, or average percentage of dead or resorbed implantations for caesarean-delivered foetuses at GD 29
- Effect level (given in dissemination database):
    - NOAEL: 175 ppm (diet) based on maternal toxicity

For F1 and litters (see **Error! Reference source not found.**):

- Viability: average number of live and dead foetuses or litter size is not affected by test substance
- Sex ratio: not affected
- Body weight: at 5,250 ppm body weight gain was decreased
- Variations/malformations:
    - increased incidences of variations (litters and foetuses), malformations (foetuses), and reversible delayed ossifications (foetuses) were seen in offspring of does treated with 5,250 ppm test substance
    - at 5,250 ppm: low incidences of hydrocephalus; enlarged and/or irregularly shaped anterior fontanelle; incomplete ossification of - or small holes in - frontals and parietals; frontals with thickened ossification; umbilical hernia; fused pulmonary artery and aorta; asymmetric and/or irregularly shaped and/or fused sternebrae; thickened areas in the ribs
    - at 5,250 ppm: foetuses had tendency to be smaller and fewer caudal vertebral, xiphoid, and forepaw phalangeal foetal ossification sites than controls
- Effect levels (given in dissemination database):
    - NOAEL: 1,750 ppm/70 mg/kg bw/d (diet) based on developmental toxicity

Table 4: Effects of tellurium exposure on mortality, body weight, and feed intake of pregnant rabbits.

Parameters	0 ppm	17.5 ppm	175 ppm	1,750 ppm	5,250 ppm
Mortality/pregnant/ number of treated females	0/11/17	0/15/17	0/11/17	0/15/17	0/14/17
No. aborted (gestation day)	1 (22)	0	2 (20, 23)	0	1 (21)
No. pregnant at Day 29, Caesarean section	10	15	9[a]	15	13
Maternal body weight (kg)					

Day 0 av (mean ± SD)	3.59 ± 0.31	3.62 ± 0.34	3.59 ± 0.34	3.62 ± 0.28	3.64 ± 0.35
Day 6 av (mean ± SD)	3.71 ± 0.29	3.75 ± 0.34	3.69 ± 0.31	3.74 ± 0.26	3.78 ± 0.35
Day 18 av (mean ± SD)	3.83 ± 0.36	3.92 ± 0.30	3.88 ± 0.35	3.54 ± 0.37	3.53 ± 0.44
Day 29 av (mean ± SD)	3.90 ± 0.33	3.97 ± 0.33	4.03 ± 0.47	3.87 ± 0.34	3.93 ± 0.44
Maternal body weight change (kg)					
Days 6-12 av	+0.08	+0.09	+0.11	-0.18**	-0.24**
Days 6-18 av	+0.12	+0.017	+0.18	-0.20**	-0.25**
Days 19-29 av	+0.13	+0.07	+0.15	+0.18	+0.17
Feed intake (g)					
Days 6-18 av	171.3	162.6	163.8	110.5*	70.5**

*Significantly different from control group (p≤0.05). **Significantly different from control group (p≤0.01). Results taken from Johnson et al. (1988).

Table 5: Effects of tellurium exposure on *in utero* development of rabbits.

Parameters	**0 ppm**	**17.5 ppm**	**175 ppm**	**1,750 ppm**	**5,250 ppm**
No. pregnant at GD 29	10	15	9	15	13
No. of live/dead foetuses	45/0	117/0	56/11	110/0	93/1
% males foetuses/litter	63.0	50.4	44.6	50.9	51.6
Mean weight (g)					
Male foetuses (mean ± SD)	46.94 ± 8.80	41.30 ± 6.62	43.41 ± 8.17	42.39 ± 7.08	39.60 ± 6. [a]
Female foetuses (mean ± SD)	42.15 ± 5.72	40.25 ± 5.20	43.30 ± 5.02	40.15 ± 4.56	39.98 ± 6. [a]
% litters/foetuses with abnormalities (mean ± SD)	7.40 ± 14.68	5.61 ± 9.01	8.13 ± 15.57	7.14 ± 26.73	16.41±22.58
No. (%) litters with abnormalities	2(22.2)	5(33.3)	2(25.0)	1(7.1)	6(46.2)
No. (%) foetuses with abnormalities	3(6.7)	6(5.1)	4(6.0)	2(1.8)	11(11.8)

Results taken from Johnson et al. (1988). a: no significance was indicated for this effect, unclear if this is a spelling mistake.

3.10.1.4 [Study 8]

Study reference:

Perez-D'Gregorio R.E., Teratogenicity of tellurium dioxide in the Wistar rat: prenatal assessment, Teratology, 37/4, 307-16, 1988

Detailed study summary and results:

Test type

In a developmental toxicity study (not according to OECD TG 414, but examinations were similar to OECD TG), rats were exposed subcutaneously to tellurium dioxide from day 15 to 19 of gestation. Information on GLP compliance is not given.

A reliability of 2 is given for this study in the registration dossier.

Test substance

- Test material used in the study is equivalent to the substance identified in the CLH dossier: tellurium dioxide
- Degree of purity: 99.9 %
- Impurities: do not affect the classification
- Batch number: Lot: 0908PH Aldrich Chemical Company
- Batch number

Test animals

- Rat/Wistar/female
- No. of animals per sex per dose: 10
- Age at the study initiation: no information available
- Weight at the study initiation: 170 – 200 g
- housing: individually, plastic cages, temperature 22 C, relative humidity 40-50 % and photoperiod (hrs dark / hrs light): 12/12

Administration/exposure

- Route of administration – subcutaneous
- Duration and frequency of test/exposure period: daily, day 15 to 19 of gestation
- Doses/concentration levels: 0, 10, 100, 500, and 1,000 µmol/kg
- Rationale for dose level selection: previously published data was taken into account. No further information given.
- Control group and treatment: yes, concurrent vehicle
- Historical control data: not provided in the dossier
- Vehicle: olive oil, 1 mL/kg maternal bw
- Test substance formulation: test substance was suspended in olive oil
- actual doses: no information available

Description of test design:

- Details on mating procedure: M/F ratios per cage: 1:1 overnight, Presence of sperm plugs in cage debris was regarded as day 0 of gestation.
- Premating exposure period for males and females (P and F1): no
- Standardization of litters: no
- Parameters assessed for P:

- mortality
- body weight: day 0, 5, 10, and daily from day 15 to 20
- gross morphological changes
- histopathology of kidney, liver, and adrenals at GD 20
- post-mortem examinations: yes
- sacrifice on day 20 of gestation
- ovaries and uterine content: yes, including gravid uterus weight, number of implantations and early/late resorptions

- Parameters assessed for F1:
  - viability (spontaneous breathing or response to tactile stimulus)
  - body weight: yes
  - sex: yes
  - recording of edema and their severity
  - recording of foetal measurements: (1) longest longitudinal dimension in natural position; (2) longest dimension occipitonasal; (3) perpendicular to 1 at the level of neck; and (4) parallel to 3 at the level of umbilical insertion
  - external examinations: yes, all per litter
  - soft tissue and skeletal examinations: yes, half per litter
  - head examinations: yes, 2 per litter
  - Post exposure observation period: no

Results and discussion

- Statistical treatment of results: A litter was regarded as an experimental unit. As a normality test the Kolmogorov-Smirnov test was used. For comparing normally distributed groups of parametric data one-way analysis of variances (ANOVA) was conducted. If a significant F-value was calculated in the ANOVA, an unpaired Student's t-test followed for determining which groups statically significant differ from controls.

For P (see **Error! Reference source not found.**):

- Mortality: two females died on third day of exposure and two on the fourth day of exposure in the highest dose group (1,000 µmol/kg), which corresponds to 40 % maternal lethality.
- Clinical signs:
- Body weight and food consumption:
  - until GD 15 body weights were similar in all groups
  - significant decrease in body weight gain was seen in dams treated with 500 µmol/kg (GD 19 onwards) and 1,000 µmol/kg (GD 18 onwards)

- Organ weights:
    - at 1,000 µmol/kg: significant decrease in gravid uterine weight
    - at 500 µmol/kg: significant increase in adrenal weight
    - at 500 µmol/kg and 1,000 µmol/kg: significant decrease in placental weight
    - liver weights were not affected
- Gross pathology: reduced sizes of renal at 1,000 µmol/kg
- Oestrous cycle: no information given
- Histopathology:
    - various degrees of centrolobular fatty change in the liver at 500 µmol/kg and 1,000 µmol/kg were observed
    - no effects on the kidneys
- Effect level (given in dissemination database):
    - NOAEL: 100 µmol/kg bw/d based on maternal toxicity

For F1 and litters (see **Error! Reference source not found.**):

- Viability:
    - mortality rates were 11 and 81 % at 500 µmol/kg and 1,000 µmol/kg
    - signs of autolysis were not observed in dead foetuses
- Sex ratio: no information available
- Body weight: dose-dependent decrease in foetal weight, but foetal/placenta weight ratio was unaffected
- Gross pathology:
    - foetal size (in particular body length) was dose-dependent significantly decreased
    - dose-related small kidneys and undescended testes in foetuses at GD 20
- Variations/malformations (see **Error! Reference source not found.**):
    - at 500 µmol/kg and 1,000 µmol/kg: measurements at level of the neck were significantly increased which indicates the presence of edema, due to observing soft tissue with many skin folds
    - at 100 µmol/kg and higher: edema, which were defined as abnormal accumulation of fluid in subcutis, were present and the severity dose-related
    - at 100 µmol/kg and higher: 100 % incidence of hydrocephalus (dilatation of cerebral ventricles) was observed. Hydrocephalus was an expansion of all cavities in the CSF pathway and an obstruction within the brain did not occur, which was determined by sagittal section of brains. In the dose groups, various dose-related degrees of hydrocephalus existed with more severe cases (cortex was thin layer) at 500 µmol/kg and 1,000 µmol/kg and moderate ventricular dilation with a thick cortical area at 100 µmol/kg

- at 500µmol/kg and 1,000 µmol/kg: open eyes were observed
- externally protruded eyes were classified as exophthalmia, sometimes ocular haemorrhage (red blood cells in tissue) also occurred
- at 100 µmol/kg: ocular haemorrhage was observed, but no open eyes
- at 500 µmol/kg and 1,000 µmol/kg: umbilical hernia (intestine in the umbilical cord and subsequent distension of this structure) could be observed in some foetuses
- skeletal analysis: no effects

- Effect levels (given in dissemination database):
  - NOAEL (male/female): 10 µmol/kg bw/d based on developmental toxicity

Table 6: Effects of tellurium exposure on maternal organ weights (in grams) of pregnant rats.

Parameters	**0 µmol/kg**	**10 µmol/kg**	**100 µmol/kg**	**500 µmol/kg**	**1,000 µmol/kg**
No. of dams	10	10	10	10	10
Uterus (mean ± SD)	72.89 ± 1.82	69.83 ± 4.34	73.69 ± 3.12	67.76 ± 3.59	41.44 ± 1.71*
Liver (mean ± SD)	14.75 ± 0.75	13.46 ± 0.58	12.06 ± 0.55	12.81 ± 0.5	12.77 ± 1.06
Left kidney (mean ± SD)	0.83 ± 0.02	0.83 ± 0.02	0.80 ± 0.03	0.83 ± 0.03	0.94 ± 0.03*
Right kidney (mean ± SD)	0.86 ± 0.02	0.87 ± 0.03	0.84 ± 0.03	0.87 ± 0.03	0.97 ± 0.04*
Left adrenal (mean ± SD)	0.041 ± 0.003	0.037 ± 0.004	0.041 ± 0.004	0.064±0.003*	0.068 ± 0.003*
Right adrenal (mean ± SD)	0.043 ± 0.003	0.039 ± 0.005	0.047 ± 0.004	0.063±0.004*	0.063 ± 0.003*

* Significantly different from control group (p≤0.01). Results taken from Perez-D'Gregorio et al. (1988).

Table 7: Effects of tellurium exposure on *in utero* development of rats.

Parameters	**0 µmol/kg**	**10 µmol/kg**	**100 µmol/kg**	**500 µmol/kg**	**1,000 µmol/kg**
No. of litters	10	10	10	10	6
Early/late resorptions	5/1	5/0	3/1	4/1	4/1
No. of live/dead foetuses	120/0	112/0	114/0	120/15	12/51
Foetal weight (g)					
live (mean ± SD)	4.06 ± 0.08	4.12 ± 0.09	3.18 ± 0.13	3.10 ± 0.11*	2.40 ± 0.28*
all (mean ± SD)	4.06 ± 0.08	4.12 ± 0.09	3.18 ± 0.13	2.96 ± 0.10*	2.45 ± 0.26*
Placental weight (grams, mean ± SD)	0.53 ± 0.02	0.53 ± 0.02	0.51 ± 0.01	0.42 ± 0.02*	0.41 ± 0.02*
Foetal/placental ratio (mean ± SD)	7.16 ± 0.79	7.88 ± 0.25	7.57 ± 0.23	7.64 ± 0.40	5.98 ± 0.49
Foetal measurements (cm)					
Body length	3.80 ± 0.02	3.79 ± 0.02	3.44 ± 0.04*	2.71 ± 0.04*	2.49 ± 0.04*
Occipito/nasal (mean ± SD)	1.69 ± 0.02	1.71 ± 0.01	1.63 ± 0.02	1.47 ± 0.03*	1.36 ± 0.03*
Neck (mean ± SD)	1.15 ± 0.02	1.10 ± 0.01	1.25 ± 0.03*	1.27 ± 0.02*	1.17 ± 0.03*
Abdomen umbilicus	1.42 ± 0.01	1.38 ± 0.01	1.45 ± 0.02	1.36 ± 0.01	1.25 ± 0.04*

Kidney length (mm, mean ± SD)					
Right kidney	3.63 ± 0.04	3.57 ± 0.05	3.23 ± 0.03	1.98 ± 0.13*	1.87 ± 0.14*
Left kidney	3.64 ± 0.05	3.46 ± 0.06	3.35 ± 0.03	2.03 ± 0.14*	1.82 ± 0.17*

* Significantly different from control group (p≤0.01). Results taken from Perez-D'Gregorio et al. (1988).

Table 8: Effects of tellurium exposure on foetuses of rats on GD 20. Data presented as number of affected/total analysed foetuses.

Parameters	0 µmol/kg	10 µmol/kg	100 µmol/kg	500 µmol/kg	1,000 µmol/kg
Undescended testis	2/54	2/51	18/52*	36/51*	29/33*
Hydrocephalus	0/120	0/120	114/114	135/135	63/63
Edema	0/120	0/120	114/114	135/135	63/63

* Significantly different from control group (p≤0.01). Results taken from Perez-D'Gregorio et al. (1988).

3.10.2 Human data

No data presented here.

3.10.3 Other data

No data presented here.

3.11 Specific target organ toxicity – single exposure

Evaluation not performed for this substance.

3.12 Specific target organ toxicity – repeated exposure

Evaluation not performed for this substance.

3.13 Aspiration hazard

Evaluation not performed for this substance.

4 ENVIRONMENTAL HAZARDS

4.1 Degradation

Evaluation not performed for this substance.

4.2 Bioaccumulation

Evaluation not performed for this substance.

4.3 Acute toxicity

Evaluation not performed for this substance.

4.4 Chronic toxicity

Evaluation not performed for this substance.

5 REFERENCES TO ANNEX I

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