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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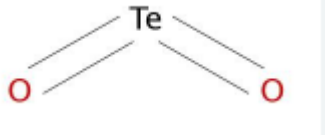
1 IDENTITY OF THE SUBSTANCE

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.

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 Dissemination, 2018)	study technically not feasible, 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 tellurium in the breast milk		(Jackson et al., 1989)
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		(Duckett, 1970)

Method	Results	Remarks	Reference
	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.		
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 tellurium is first reduced to telluride (Te^{2-}) and thereafter methylated Solubility of tellurium dioxide in		(ECHA Dissemination, 2018)

Method	Results	Remarks	Reference
	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:

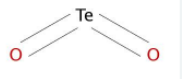
- NN (2012) reported from ECHA Dissemination (2018): Bacterial Reverse Mutation Assay performed with tellurium
- Johnson et al. (1988): Data on developmental toxicity of tellurium in rats and rabbits
- Agnew and Curry (1972); Agnew et al. (1968): Data on developmental toxicity of tellurium in rats
- 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.) **Repr. 1B** (H360: May damage fertility or the unborn child.) **Aquatic Chronic 4** (H413: May cause long lasting harmful effects to aquatic life.)	**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.)

[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
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		
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

	Source substance	Target substance
Chemical name	Tellurium	Tellurium dioxide
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.

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				

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
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 sex and dose group RL1 (according to registration dossier and the authors of this document)	Tellurium dioxide (information on purity: see confidential annex) 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. Application via gavage, 7 days/week	<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), - 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);	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
	Vehicle: 1 % (v/v) methyl cellulose solution	- in males no effects on reproductive function, weight and histopathology of reproductive organs or sperm parameter were observed up to the highest dose. F1: 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	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)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
document)				

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	Tellurium dioxide (Purity: 99.99%) 0, 10, 100, 500, 1000 µmol TeO_2/kg	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	(Perez-D'Gregorio and Miller, 1988) also reported in

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
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)	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	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.	(ECHA Dissemination, 2018) (Perez-D'Gregorio et al., 1988) also reported in (ECHA Dissemination, 2018)
Reproduction / Developmental Toxicity Screening Test OECD TG 421 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)	Tellurium dioxide (information on purity: see confidential annex) 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. Application via gavage, 7 days/week Vehicle: 1 % (v/v) methyl cellulose	Effects on parental animals see section 10.10.1 <u>Offspring:</u> LOAEL: 25 TeO_2 mg/kg bw/d (increased pup mortality at all dose groups) 600 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 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	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
	solution	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; foetuses and dams were sacrificed on 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 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**
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 dossier and the authors of this document)	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 solution, examination for hydrocephalus (increased ventricular dilatation	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
	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) RL4 (according to registration dossier and the authors of this	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 3-5 days before delivery Dams were allowed to deliver and	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
document)	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 registration dossier and the authors of this document)	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 removed via abdominal wall; after closing the wall the dams were allowed to deliver;	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
	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 Application via diet	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)
Investigations on the mechanism	Read-across substance tellurium	Mechanistic study, investigation on the tellurium-induced effect on squalene	Inhibition of cholesterol synthesis and accumulation of squalene in different	(Wagner et al., 1995)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
of tellurium induced neuropathy *In vivo* and *in vitro* studies, not following any guideline	(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	epoxidase in sciatic nerves and liver	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.	

* 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) RL3 (according to the authors of this document)	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 examinations of pups: light and electron microscopic investigations of spinal cord,	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
	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.

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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