Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

tellurium dioxide

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

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

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

Contact details for dossier submitter:

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

CONTENTS

1 PHYSICAL HAZARDS

1.1 Explosives

Evaluation not performed for this substance.

1.2 Flammable gases (including chemically unstable gases)

Evaluation not performed for this substance.

1.3 Oxidising gases

Evaluation not performed for this substance.

1.4 Gases under pressure

Evaluation not performed for this substance.

1.5 Flammable liquid

Evaluation not performed for this substance.

1.6 Flammable solids

Evaluation not performed for this substance.

1.7 Self-reactive substances

Evaluation not performed for this substance.

1.8 Pyrophoric liquids

Evaluation not performed for this substance.

1.9 Pyrophoric solid

Evaluation not performed for this substance.

1.10 Self-heating substances

Evaluation not performed for this substance.

1.11 Substances which in contact with water emit flammable gases

Evaluation not performed for this substance.

1.12 Oxidising liquids

Evaluation not performed for this substance.

1.13 Oxidising solids

Evaluation not performed for this substance.

1.14 Organic peroxides

Evaluation not performed for this substance.

1.15 Corrosive to metals

Evaluation not performed for this substance.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No relevant data available for this endpoint.

3 HEALTH HAZARDS

Acute toxicity

3.1 Acute toxicity - oral route

Evaluation not performed for this substance.

3.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

3.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

3.4 Skin corrosion/irritation

Evaluation not performed for this substance.

3.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

3.6 Respiratory sensitisation

Evaluation not performed for this substance.

3.7 Skin sensitisation

Evaluation not performed for this substance.

3.8 Germ cell mutagenicity

3.8.1 In vitro data

3.8.1.1 [Study 1]

Study reference:

Study report, 2012 [confidential]

Detailed study summary and results:

Test type

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

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

Test substance

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

Administration/exposure

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

Results and discussion

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

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

3.8.1.2 [Study 2]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

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

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

Test substance

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

Administration/exposure

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

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

Results and discussion

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

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

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

3.8.1.3 [Study 3]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

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

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

Test substance

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

Administration/exposure

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

Results and discussion

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

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

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

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

3.8.1.4 [Study 4]

Study reference:

Study report, 2012 [confidential]

Detailed study summary and results:

Test type

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

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

Test substance

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

Administration/exposure

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

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

Results and discussion

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

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

3.8.2 Animal data

No data presented here.

3.8.3 Human data

No data presented here.

3.8.4 Other data

No data presented here.

3.9 Carcinogenicity

No relevant data available for this endpoint.

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 [Study 5]

Study reference:

Study report, 2013 [confidential]

Detailed study summary and results:

Test type

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

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

Test substance

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

Test animals

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

Administration/exposure

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

Description of test design:

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

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

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

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

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

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

Results and discussion

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

For P:

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

in females were about 5 and 11 % lower than controls, respectively (during pregnancy the effect was more pronounced), and at termination body weight in females were about 18 and 30 % below controls, respectively
    - 25 mg/kg bw/d: no treatment-related effects
    - food consumption: reduction in line with body weight effects
- Mating procedure:
    - 600 mg/kg bw/d: duration of mating period was significantly affected; for 2 females no successful coitus was observed during 14 d mating period (usually successful coitus occurred within 5 days) and one deceased female without successful coitus was found on day 13 of mating period
- Oestrous cycle:
    - 600 mg/kg bw/d: mainly diestrus phases characterised the oestrous cycle of animals
- Sperm examination:
    - no difference between highest dose group and controls for male gonads, testicular interstitial cell structure, spermatogenic cells (development and differentiation), and microscopic changes in reproductive organs
    - 600 mg/kg bw/d: unilateral distribution of testicular observation, not treatment-related
- Reproductive indices:
    - 600 mg/kg bw/d: mating indices reduced with 73 %, compared to 100 % in control, low and mid dose groups
    - 600 mg/kg bw/d: fertility indices reduced with 63 % (3/11 non-pregnant females), compared to 100 % in control, low and mid dose groups
    - 600 mg/kg bw/d: gestation index reduced with 0 %, compared to 92 % in control (one animal with stillborns, considered as incidental), 100 % in low and 67 % in mid (2/12 animals with stillborns) dose groups
- Organ weights:
    - Males: weights of seminal vesicles as absolute and relative weights (adjusted to brain weight) were statistically significant decreased ($p<0.05$) at 600 mg/kg bw/d compared to controls, no histological evidence for effects on male reproductive system was seen, further statistical differences in organ weights were assigned to body weight differences
    - Females: mean absolute weight of vagina was statistically significantly decreased ($p<0.01$) at 600 mg/kg bw/d compared to controls (47 % below controls), probably related to ovary atrophy due to sensitivity of vagina weight to altered ovarian hormone production, further statistical differences in relative organ weights were observed, but assigned to body weight differences (see section on body weight)
- Gross pathology

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

- Liver: vacuolation of hepatocytes containing predominantly large well-defined round vacuoles with displaced nuclei to the periphery, necrotic processes of the liver are characterised by lysis of nuclei and increased eosinophilia of cytoplasm
- severity and incidence of treatment-related microscopic effects were dose-dependent
- 120 mg/kg bw/d in females: only liver was affected
- 120 and 600 mg/kg bw/d in males: dose-related accumulation of pigmented macrophages in mesenteric lymph nodes was observed and confirmed at necropsy

- Effect levels (given in dissemination database[1]):
  - NOAEL (male): 600 mg/kg bw/d, based on no effects on male reproductive system
  - NOAEL (female): 25 mg/kg bw/d, based on effects on female reproductive system at 120 and 600 mg/kg bw/d
  - NOAEL (male/female): 25 mg/kg bw/d, based on systemic effects in parental animals

For F1 and litters:

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

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

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

3.10.1.2 [Study 6]

Study reference:

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

Detailed study summary and results:

Test type

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

Test substance

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

Test animals

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

Administration/exposure

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

Description of test design:

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

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

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

Results and discussion

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

For P:

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

For F1 and litters:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.10.1.3 [Study 7]

Study reference:

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

Detailed study summary and results:

Test type

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

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

Test substance

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

Test animals

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

Administration/exposure

- Route of administration – oral (feed)

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

Description of test design:

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

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

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

Results and discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

3.10.1.4 [Study 8]

Study reference:

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

Detailed study summary and results:

Test type

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

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

Test substance

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

Test animals

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

Administration/exposure

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

Description of test design:

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

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

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

Results and discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.10.2 Human data

No data presented here.

3.10.3 Other data

No data presented here.

3.11 Specific target organ toxicity – single exposure

Evaluation not performed for this substance.

3.12 Specific target organ toxicity – repeated exposure

Evaluation not performed for this substance.

3.13 Aspiration hazard

Evaluation not performed for this substance.

4 ENVIRONMENTAL HAZARDS

4.1 Degradation

Evaluation not performed for this substance.

4.2 Bioaccumulation

Evaluation not performed for this substance.

4.3 Acute toxicity

Evaluation not performed for this substance.

4.4 Chronic toxicity

Evaluation not performed for this substance.

5 REFERENCES TO ANNEX I

Johnson, E.M.; Christian, M.S.; Hoberman, A.M.; DeMarco, C.J.; Kilpper, R.; Mermelstein, R. (1988)
Developmental toxicology investigation of tellurium
Fundamental and Applied Toxicology, 11, 691-702

Perez-D'Gregorio, R.E.; Miller, R.K. (1988)
Teratogenicity of tellurium dioxide: prenatal assessment
Teratology, 37, 307-316