**SIDS Dossier**

**OECD HPV Chemical Programme, SIDS Dossier, approved at CoCAM 1 (10/10/2011)**

|  |  |
| --- | --- |
| **Printing Date** | 2011-12-01 10:27:57 JST |

|  |
| --- |
| **Restriction of specific regulatory purposes** |
|  |
| **Confidentiality** |
|  |

|  |  |
| --- | --- |
| **Name** | (JP) 1,1,1-Tris(hydroxymethyl)ethane |
| **Legal entity owner** | National Institute of Health Sciences / Tokyo / Japan |

**Substance: (JP) 1,1,1-Tris(hydroxymethyl)ethane**

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-62beb752-d6a7-4061-b7c2-140340e0729d |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:27:31 JST |
| **Remarks** |  |  |

**0 Related Information**

**0.1 Templates**

**0.2 Categories**

**0.3 Mixtures**

**1 General Information**

**1.1 Identification**

**Substance identification**

|  |  |
| --- | --- |
| **Chemical name** | (JP) 1,1,1-Tris(hydroxymethyl)ethane |
| **Legal entity** | [National Institute of Health Sciences / Tokyo / Japan](file:///C:\IUCLID5\5.3.0\index.html#IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101/0) |

**Reference substance**

|  |
| --- |
| [1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- / 1,1,1-Tris(hydroxymethyl)ethane / 77-85-0](file:///C:\IUCLID5\5.3.0\index.html#IUC5-3306ca57-7e96-4ef8-a4d6-dcf703b6501d/0) |
| |  |  | | --- | --- | | **EC number** | **EC name** | | 201-063-9 | ethylidynetrimethanol | | **CAS number** | **CAS name** | | 77-85-0 | 1,1,1-Tris(hydroxymethyl)ethane | | **IUPAC name** | | |  | | |

**Type of substance**

|  |  |
| --- | --- |
| **Composition** | mono constituent substance |
| **Origin** | organic |

**Trade names**

|  |  |
| --- | --- |
| **Name** | 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- |
| **Name** | 1,1,1-Trimethylolethane |
| **Name** | Trimethylolethane |
| **Name** | Ethylidynetrimethanol |
| **Name** | Ethane, 1,1,1-tris(hydroxymethyl)- |
| **Name** | Methriol |
| **Name** | Methyltrimethanolmethane |
| **Name** | Metriol |

**1.2 Composition**

**1.3 Identifiers**

**1.4 Analytical information**

**1.5 Joint submission**

**1.6 Sponsors**

**1.7 Suppliers**

**1.8 Recipients**

**1.9 Product and process oriented research and development**

**2 Classification and Labelling**

**2.1 GHS**

**2.2 DSD - DPD**

**3 Manufacture, use and exposure**

**3.1 Technological process**

**Technological process**

|  |  |  |
| --- | --- | --- |
| |  |  | | --- | --- | | **Methods of manufacture** | 1,1,1-Tris(hydroxymethyl)ethane is produced by aldol condensation of propionaldehyde with formaldehyde, followed by reaction of the intermediate 2,2-bis(hydroxymethyl)propanal with excess formaldehyde in the presence of sodium hydroxide or lime as basic component. | |

**3.2 Estimated quantities**

**Estimated quantities**

|  |  |  |
| --- | --- | --- |
| |  | | --- | | **Remarks** | | Currently, no production of 1,1,1-tris(hydroxymethyl)ethane is reported in Japan (sponsor country) and import volume in Japan is between 100 and 1,000 tonnes/year. | |

**3.3 Sites**

**3.4 Form in the supply chain**

**3.5 Identified uses**

**3.6 Uses advised against**

**3.7 Waste from production and use**

**3.8 Exposure estimates**

**3.9 Biocidal information**

**3.10 Application for authorisation of uses**

**4 Physical and chemical properties**

**4.1 Appearance/physical state/colour**

***Endpoint study record: Literature***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-5af539db-6723-4eb4-8f31-db0418d5fa17 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:10 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | other: |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable handbook | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| review article or handbook | Lide D.R. (ed) | 2008 | CRC Handbook of Chemistry and Physics, version 2008. |  |  |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussion**

**Physical state at 20ºC and 1013 hPa**

|  |
| --- |
| solid |

**Form**

|  |
| --- |
| powder |

**Colour**

|  |
| --- |
| White |

**Odour**

|  |
| --- |
| odourless |

**Substance type**

|  |
| --- |
| organic |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| 1,1,1-Tris(hydroxymethyl)ethane is white powder with no odour. |

**4.2 Melting point/freezing point**

***Endpoint study record: Literature***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-c11b35db-58dc-48be-8311-6bf3800fc268 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:10 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | other: |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable handbook | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| review article or handbook | Lide D.R. (ed) | 2008 | CRC Handbook of Chemistry and Physics, version 2008. |  |  |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussions**

**Melting / freezing point**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Melt./Freez. pt.** | **Atm. pressure** | **Decomposition** | **Decomp. temp.** | **Sublimation** | **Subl. temp.** | **Remarks** |
| 204 °C |  |  |  |  |  |  |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Melting point is 204 degree C. |

***Endpoint study record: Literature***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-42070fd1-10fe-48e2-b78e-29b093f743f7 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:10 JST |
| **Remarks** |  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | supporting study; robust study summary | | |
| **Study result type** | other: |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable handbook | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| review article or handbook | James G. Speight | 2005 | Lange's Handbook of Chemistry, 16th edition |  |  |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Results and discussions**

**Melting / freezing point**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Melt./Freez. pt.** | **Atm. pressure** | **Decomposition** | **Decomp. temp.** | **Sublimation** | **Subl. temp.** | **Remarks** |
| > 200 — < 203 °C |  |  |  |  |  |  |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Melting point is 200-203 degree C. |

**4.3 Boiling point**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-7277aeb0-57e3-4bc1-b884-967e2955f172 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:11 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 2010 |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted according to OECD test-guideline in compliance with GLP. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Evaluation and Research Institute, Japan | 2010 | Measurement of boiling point of 2-metyl-2-hydroxymethyl-1,3-propanediol (K-1087); Photocell detection method |  | Chemicals Evaluation and Research Institute, Japan |  |  | 805775 | 2010-11-29 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Type of method**

|  |
| --- |
| photocell detection |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Trimethylolethane - Analytical purity: 99.4% - Impurities (identity and concentrations): Not mentioned - Lot/batch No.: 7UNEG - Stability under test conditions: IR chromatogrammes were measured before and after the experiment. - Storage condition of test material: Dark cool place |

**Any other information on materials and methods incl. tables**

|  |
| --- |
| Test conditions  - Apparatus; Melting Point M-565 (BUCHI Labotechnique)  - Sample tube; External diameter: 3.0 mm, internal diameter: 80 mm Capillary tube; Internal diameter: 1.0 mm, thickness of tube; 0.2 mm- Number of replicates; 2 |

**Results and discussions**

**Boiling point**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Boiling pt.** | **Atm. pressure** | **Decomposition** | **Decomp. temp.** | **Remarks** |
| 286.7 °C |  |  |  |  |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Boiling point of 1,1,1-tris(hydroxymethyl)ethane   |  |  |  | | --- | --- | --- | | No. | Measured value (degree C) | Mean (degree C) | | 1 | 286.4 | 286.7 | | 2 | 587.0 | |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Boiling point is 286.7 degree C. |

***Endpoint study record: Literature***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-5d8ab8fc-cb69-4a62-8d7f-1b0ab7b3fb93 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:11 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | supporting study; robust study summary | | |
| **Study result type** | other: |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable handbook | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| review article or handbook | Lide D.R. (ed) | 2008 | CRC Handbook of Chemistry and Physics, version 2008. |  |  |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Results and discussions**

**Boiling point**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Boiling pt.** | **Atm. pressure** | **Decomposition** | **Decomp. temp.** | **Remarks** |
| 136 °C | 15 mm Hg |  |  |  |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Boiling point at 15 mm Hg is 136 degree C. |

**4.4 Density**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-9202e03a-3445-4c2b-a8a6-01a6f1524d85 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:11 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 1993 |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted in accordance with equivalent protocol with OECD test guideline. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Inspection & Testing Institute, Japan | 1993 | Measurement of physico-chemical properties of 2-metyl-2-hydroxymethyl -1,3-propanediol (K-1087) |  | Chemicals Inspection & Testing Institute, Japan | 81087K |  |  | 1993-05-21 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | other guideline: JIS K 7112-1980 |  |

**Type of method**

|  |
| --- |
| pycnometer method |

**GLP compliance**

|  |
| --- |
| no |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussion**

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Density;   |  |  |  | | --- | --- | --- | | No. of replicates | Measured value (g/cm3) | Mean (g/cm3) | | 1 | 1.232 | 1.236 | | 2 | 1.237 | | 3 | 1.239 |   Temperature: 25 ± 0.5 degree C |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Density is 1.236 g/cm3 at 25 degree C. |

**4.6 Vapour pressure**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-7de3cc1d-b3f0-4ae2-8dec-063885c06f34 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:12 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 2011 |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted according to OECD test-guideline in compliance with GLP. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Evaluation and Research Institute, Japan | 2011 | Measurement of water solubility of 2-metyl-2-hydroxymethyl-1,3-propanediol (K-1087); Flask method |  | Chemicals Evaluation and Research Institute, Japan | 805777 |  |  | 2011-01-27 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 104 (Vapour Pressure Curve) | no |

**Type of method**

|  |
| --- |
| gas saturation method |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Trimethylolethane - Analytical purity: 99.4 % - Lot/batch No.: 7UNEG - Stability under test conditions: IR chromatogramms were measured before and after the experiment. - Storage condition of test material: Dark cool place |

**Any other information on materials and methods incl. tables**

|  |
| --- |
| Test conditions  Apparatus; Vaour pressure tester (Gas saturation method)  Sample tube; Glass tube packed with glass porous beads coated by test material  Temperature; 80, 85 and 90 degree C  Carrier gas; High purity nitrogen gas  Flow rate; 20, 30 and 40 mL/min  Number of replicates; 1  Trapping solvent; 30 mL of water  Analytical method; LC-MS |

**Results and discussions**

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Measured value   |  |  |  |  | | --- | --- | --- | --- | | Temperature (degree C) | Flow rate (mL/min) | Vapour pressure (Pa) | | | Measured value | Mean value | | 80 | 20  30  40 | 3.48 x 10-2  3.71 x 10-2  2.93 x 10-2 | 3.38 x 10-2 | | 85 | 20  30  40 | 6.57 x 10-2  5.68 x 10-2  6.23 x 10-2 | 6.16 x 10-2 | | 90 | 20  30  40 | 9.95 x 10-2  1.11 x 10-1  1.00 x 10-1 | 1.04 x 10-1 |   Regression equation;  lop P (Pa) = -6262.32/T + 16.2640  Vapour pressure at 25 degree C is calculated to be 1.82 x 10-5Pa according to the regression equation. |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Vapour pressure at 25 degree C is 1.82E-5 Pa |

**4.7 Partition coefficient**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-2feb080e-0603-499a-a480-33fd86bec40e |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:12 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 1994 |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted according to OECD test-guideline in compliance with GLP. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Inspection & Testing Institute, Japan | 1994 | Study of partition coefficient of 2-metyl-2-hydroxymethyl-1,3-propanediol (K-1087) between water and 1-octanol |  | Chemicals Inspection & Testing Institute, Japan | 81087K |  |  | 1994-07-27 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Partition coefficient type**

|  |
| --- |
| octanol-water |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method) | no |

**Type of method**

|  |
| --- |
| shake-flask method |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Analytical purity: 99.6 % - Lot/batch No.: 05025EW - Storage condition of test material: Cool and dark place |

***Analytical method***

|  |
| --- |
| GC |

***Details on methods***

|  |
| --- |
| - Amount of test substance introduced in the test vessels: 19.9 mg - Volume of each phase in each vessel: Condidion 1: Otanol 5 mL, Water 30 mL, Condition 2: Octanol 10 mL, Water 25 mL, Condition 3: Octanol 20 mL, Water 15 mL - Analytical procedures: Test material was quantitatively analyzed by GC after dilution by methanol. |

**Results and discussions**

**Partition coefficient**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Partition coefficient** | **Temp.** | **pH** | **Remarks** |
| log Pow | -0.95 | 25 °C | 6.9 |  |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Partition coefficient   |  |  |  |  | | --- | --- | --- | --- | |  | Log Kow | | Average | | a | b | | Condition 1 | -0.94 | -0.97 | -0.95 | | Condition 2 | -0.93 | -0.98 | | Condition 3 | -0.97 | -0.91 |   pH of water phase   |  |  |  | | --- | --- | --- | |  | pH | | | a | b | | Condition 1 | 6.9 | 6.9 | | Condition 2 | 6.9 | 7.0 | | Condition 3 | 6.9 | 7.0 | |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Partition coefficient between octanol and water (Log Kow) is -0.95. |

**4.8 Water solubility**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-fd0415cf-31ab-475c-b2c1-091fdbb92b43 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:12 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 2010 |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted according to OECD test-guideline in compliance with GLP. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Evaluation and Research Institute, Japan | 2010 | Measurement of water solubility of 2-metyl-2-hydroxymethyl-1,3-propanediol (K-1087); Flask method |  | Chemicals Evaluation and Research Institute, Japan | 805777 |  |  | 2010-12-02 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 105 (Water Solubility) | no |

**Type of method**

|  |
| --- |
| flask method |

**GLP compliance**

|  |
| --- |
| no |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Trimethylolethame - Analytical purity: 99.4 % - Lot/batch No.: 7UNEG - Storage condition of test material: Cool and dark place. |

***Details on methods***

|  |
| --- |
| Limit test was conducted because water solubility of test material was high. Test condition Test media; purified water Temperature; 20 +/- 0.5 degree C Number of replicates; 2 |

**Results and discussions**

**Water solubility**

|  |  |
| --- | --- |
| >= 300 g/L | |
| **Temp.** | 20 °C |

**Applicant's summary and conclusion**

**Interpretation of results**

|  |
| --- |
| very soluble (> 10000 mg/L) |

**Conclusions**

|  |
| --- |
| Water solubility is equal to or more than 300 g/L. |

**5 Environmental fate and pathways**

**5.1 Stability**

**5.1.1 Phototransformation in air**

***Endpoint study record: QSAR***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-f0662f0e-ab82-4294-8e95-6677b4ff5ec6 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:07 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | (Q)SAR |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable QSAR method | | |

**Materials and methods**

**Principles of method if other than guideline**

|  |
| --- |
| AOPWIN (version 1.92a) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Study design**

***Estimation method (if used)***

|  |
| --- |
| PHOTOCHEMICAL REACTION WITH OH RADICALS- Concentration of OH radicals: 1.5E6 molecule/cm3- Computer programme: AOPWIN (version 1.92a) |

**Results and discussions**

**Any other information on results incl. tables**

|  |
| --- |
| Rate constant of12.6E-12 cm3/molecule-sec |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Half-life time for the indirect photo-oxidation by reaction with hydroxyl radicals is 0.85 days by AOPWIN (version 1.92a). |

**5.1.2 Hydrolysis**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-921e2ac8-60af-4fc0-970e-4fd8b79ec6b6 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:07 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 1998 |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted in accordance with OECD test-guideline. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Inspection & Testing Institute, Japan | 1998 | Measurement of physico-chemical properties of 2-metyl-2-hydroxymethyl -1,3-propanediol (K-1087) |  | Chemicals Inspection & Testing Institute, Japan | 81087K |  |  | 1998-02-13 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**GLP compliance**

|  |
| --- |
| no |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Analytical purity: 97.1 % - Lot/batch No.: WTL0646 |

**Study design**

**Duration of test**

|  |  |  |  |
| --- | --- | --- | --- |
| 5 d | | | |
| **pH** | pH4, pH7, pH9 | **Temp.** | 50 +/- 1 degree C |

***Number of replicates***

|  |
| --- |
| 2 |

**Results and discussion**

**Any other information on results incl. tables**

|  |
| --- |
| Test substance was stable at 50 degree C for five days at pH 4, 7 and |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| 1,1,1-Tris(hydroxymethyl)ethane is not hydrolyzed. |

**5.2 Biodegradation**

**5.2.1 Biodegradation in water: screening tests**

***Endpoint study record: Experiment***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-b9a48f2a-56fa-4017-8478-67be138d2ac4 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:08 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | experimental result | **Study period** | 1993 |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | Test was conducted according to OECD test-guideline in compliance with GLP. | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | Chemicals Inspection & Testing Institute, Japan | 1993 | Measurement of physico-chemical properties of 2-metyl-2-hydroxymethyl -1,3-propanediol (K-1087) |  | Chemicals Inspection & Testing Institute, Japan | 81087K |  |  | 1993-06-30 |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test type**

|  |
| --- |
| ready biodegradability |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I)) | no |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 2-methyl-2-hydroxymethyl-1,3-propanediol - Analytical purity: 99.6 % - Lot/batch No.: 05025EW - Stability under test conditions: IR chromatogrammes were measured before and after the experiment. - Storage condition of test material: Cool and dark place |

**Study design**

**Oxygen conditions**

|  |
| --- |
| aerobic |

**Inoculum or test system**

|  |
| --- |
| activated sludge, non-adapted |

***Details on inoculum***

|  |
| --- |
| From 10 different places including sewage treatment plants, rivers, lake and inner sea in Japan, sludge and environmental water and soil were collected in March 1993. Concentration of the sludge was 30 mg/L as suspended solid matters. |

**Duration of test (contact time)**

|  |
| --- |
| 28 d |

**Initial test substance concentration**

|  |  |
| --- | --- |
| **Initial conc.** | **Based on** |
| 100 mg/L | test mat. |

***Details on analytical methods***

|  |
| --- |
| DETAILS ON PRETREATMENT After the cultivation period, 10 mL of the test solution was taken out and this portion was centrifuged with 1000xg for ten minutes. Then the supernatant was used for TOC analysis and direct analysis by GC.  GC condition - Column: 20 mm x 1.2 mm ID, glass column - Detection method: FID - Flow rate: 20 mL/min - Injection volume: 1 uL |

***Details on study design***

|  |
| --- |
| 6 bottles were prepared, which are as follows. - [Water + Test substance] - [Test medium + Test substance + Sludge] -1 - [Test medium + Test substance + Sludge] -2 - [Test medium + Test substance + Sludge] -3 - [Test medium + Sludge]  Volume of test medium or water: 300 mL Volume of the test substance added was 30 mg which is injected with 29. 5 uL by micro-syringe. BOD was continuously measured by BOD meter over the cultivation period. |

***Reference substance***

|  |
| --- |
| aniline |

**Results and discussions**

**% Degradation of test substance**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **%Degr.** | **St. dev.** | **Parameter** | **Sampling time** | **Remarks** |
| > 3 — < 6 |  | O2 consumption | 28 d |  |

**Details on results**

|  |
| --- |
| Degradability of Aniline is 67 % after 7 days and 71 % after 14 days. |

**BOD5 / COD results**

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Result of analysis after 28 -day.   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | |  | | [Water + test substance] | [Test medium + Test substance + Sludge] -1 | [Test medium + Test substance + Sludge] -2 | [Test medium + Test substance + Sludge] -3 | Theoretical amount  (mg) | | BOD | mg | 0.0 | 1.4 | 2.2 | 3.3 | 51.9 | | Residue by DOC | mg | 15.1 | 14.7 | 14.8 | 15.1 | 15.0 | | % | 101 | 98 | 99 | 101 | | Residue by direct analysis (GC) | mg | 29.4 | 29.2 | 29.4 | 29.2 | 30 | | % | 98 | 97 | 98 | 97 |   Degradation after 28 -day   |  |  |  |  | | --- | --- | --- | --- | |  | [Test medium + Test substance + Sludge] -1 | [Test medium + Test substance + Sludge] -2 | [Test medium + Test substance + Sludge] -3 | | Degradation by BOD | 3 | 4 | 6 | | Degradation by TOC | 3 | 2 | 0 | | Degradation by GC | 1 | 0 | 1 | |

**Applicant's summary and conclusion**

**Interpretation of results**

|  |
| --- |
| under test conditions no biodegradation observed |

**Conclusions**

|  |
| --- |
| Biodegradation of 1,1,1-Tris(hydroxymethyl)ethane by BOD was 3-6 % according to OECD Test guideline 301C. |

**5.3 Bioaccumulation**

**5.3.1 Bioaccumulation: aquatic / sediment**

***Endpoint study record: QSAR***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-d683f21c-e981-4984-a966-cbfc545b0948 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:08 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | (Q)SAR |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable QSAR method | | |

**Materials and methods**

**Principles of method if other than guideline**

|  |
| --- |
| BCFBAFWIN (version 3.00) with log Kow of 1.67 |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussions**

**Bioaccumulation factor**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Conc. in environment / dose** | **Type** | **Value** | **Basis** | **Time of plateau** | **Calculation basis** | **Remarks** |
|  | BCF | 3.2 |  |  |  | BCFBAFWIN(version 3.00) with Log Kow of -0.95 |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Bio-concentration factor is 3.1 by MPBPWIN (version 3.00). |

**5.4 Transport and distribution**

**5.4.1 Adsorption / desorption**

***Endpoint study record: QSAR***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-e6ca8a16-2d0b-4a64-8531-6c5d15a05086 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:09 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | (Q)SAR |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable QSAR method | | |

**Materials and methods**

**Principles of method if other than guideline**

|  |
| --- |
| KOCWIN (version 2.00) |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussions**

**Adsorption coefficient**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Value** | **Temperature** | **% Org. carbon** | **Remarks** |
| log Koc | -0.4 |  |  | KOCWIN(version 2.00) with Log Kow of -0.98 |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Soil adsorption coeffiicent (log Koc) is -0.4 by KOCWIN (version 2.00). |

**5.4.2 Henry's Law constant**

***Endpoint study record: QSAR***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-32bd338b-311a-42e1-9c6a-1b51ca940115 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:09 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | (Q)SAR |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable QSAR | | |

**Materials and methods**

**Principles of method if other than guideline**

|  |
| --- |
| HENRYWIN (version 3.20), bond estimation method |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Results and discussions**

**Henry's Law constant H**

|  |  |
| --- | --- |
| **H** | 0.00113 Pa m³/mol |
| **Temp. (°C)** | 25 |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| Henry's law constant is 1.13E-3 Pa.m3/mole by HENRYWIN (version 3.20). |

**5.4.3 Distribution modelling**

***Endpoint study record: QSAR***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-1c3d206a-ff70-4c6d-964c-a44c2b401d94 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:09 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study; robust study summary | | |
| **Study result type** | (Q)SAR |  |  |
| **Reliability** | 2 (reliable with restrictions) | | |
| **Rationale for reliability incl. deficiencies** | Reliable QSAR | | |

**Materials and methods**

**Model**

|  |
| --- |
| Calculation according to Mackay, Level III |

**Calculation programme**

|  |
| --- |
| EPISUITE (version 4.0) |

**Release year**

|  |
| --- |
| 2008 |

**Media**

|  |
| --- |
| air - biota - sediment(s) - soil - water |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

***Test substance input data***

|  |
| --- |
| - Water solubility: 300 g/L (the lowest limit value) - Vapour pressure: 1.82E-5 Pa - log Pow: -0.95 - Melting point: 204 degree C - Boiling point: 286.7 degree C - Henry's Law constant: 1.13E-3 Pa.m3/mole |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| When equal and continuous release to air, water and soil is assumed, 1,1,1-Tris(hydroxymethyl)ethane is mainly distributed in water and soil compartments. |

**Executive summary**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Environmental distribution of 1,1,1-tris(hydroxymethyl)ethane with Fugacity Level III model   |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | Release to air, water and soil | Release to air | Release to water | Release to soil | | Air compartment | 0.3 % | 0.7 % | 0.0 % | 0.0 % | | Watercompartment | 38.7 % | 24.7 % | 99.8 % | 20.9 % | | Soil compartment | 61.0 % | 74.6 % | 0.0 % | 79.0 % | | Sediment compartment | 0.1 % | 0.0 % | 0.2 % | 0.0 % | |

**6 Ecotoxicological Information**

**6.1 Aquatic toxicity**

**6.1.1 Short-term toxicity to fish**

***Endpoint study record: MOE\_Acute toxicity to fish.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-a229136f-8e52-49b9-a275-2e6a1ff625f0 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-29 18:56:13 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MOE, Japan | 1998 | Ecotoxicity of 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- for aquatic species of algae, daphnia and fish. | Unpublished |  |  |  |  |  |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 203 (Fish, Acute Toxicity Test) |  |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material: 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl-  - Purity: 97.1 %  - Stability: IR absorption spectrum of the chemical was taken at the start and the end of the test, and both spectrums were not contradictory to each other.  - Storage condition of test material: Stored in a refrigerator. |

**Analytical monitoring**

|  |
| --- |
| yes |

***Details on sampling***

|  |
| --- |
| - Concentrations: All concentrations were measured at the start and at just before water exchange (after 24-hour) during test period. |

***Details on analytical methods***

|  |
| --- |
| IDENTIFICATION AND QUANTIFICATION OF TEST SUBSTANCE/PRODUCT - Separation method (e.g. HPLC, GC): GC. |

**Vehicle**

|  |
| --- |
| no |

***Details on test solutions***

|  |
| --- |
| PREPARATION AND APPLICATION OF TEST SOLUTION (especially for difficult test substances) - Method: Stock solution (concentration of 10000 mg/L) was prepared by diluting the test chemical with pure water. |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| Oryzias latipes |

***Details on test organisms***

|  |
| --- |
| TEST ORGANISM - Source: Obtained from a private fish farm in Japan.  - Length at study initiation (length definition, mean, range and SD): total length, 1.83 cm (1.56 – 2.19 cm, n=10).  - Weight at study initiation (mean and range, SD): wet weight, 0.111 g (0.058 – 0.186 g, n=10).   - Feeding during test: None  ACCLIMATION - Acclimation period: More than 36 days before testing.  - Acclimation conditions (same as test or not): Same as test.  - Type and amount of food: TETRAMIN, 1-2% of body weight per a day.  - Feeding frequency: once a day, starved for 24 hours before the test started.  - Health during acclimation (any mortality observed): The mortality of the test organisms for 7 days before testing was not greater than 5 %. |

**Study design**

**Test type**

|  |
| --- |
| semi-static |

**Water media type**

|  |
| --- |
| freshwater |

**Limit test**

|  |
| --- |
| yes |

**Total exposure duration**

|  |
| --- |
| 96 h |

**Test conditions**

***Hardness***

|  |
| --- |
| 63 mg/L (as CaCO3) (dilution water) |

***Test temperature***

|  |
| --- |
| 24 +/- 1 C (setting) 23.6 - 24.2 C (during test period) |

***pH***

|  |
| --- |
| 7.8 (dilution water)  7.1 - 7.6 (during test period) |

***Dissolved oxygen***

|  |
| --- |
| 6.4 - 8.7 mg/L (more than 60% of saturation) (during test period) |

***Nominal and measured concentrations***

|  |
| --- |
| Nominal concentrations: Control and 100 mg/L (limit test).  Mean measured concentrations: 89.4 mg/L (geometric mean) |

***Details on test conditions***

|  |
| --- |
| TEST SYSTEM - Test vessel: 5.0 L test solution in a 5 L glass beaker.  - Aeration: None. - Renewal rate of test solution (frequency/flow rate): Every 24 hours.  - No. of organisms per vessel: 10.  - No. of vessels per concentration (replicates): 1.  - No. of vessels per control (replicates): 1.   TEST MEDIUM / WATER PARAMETERS - Source/preparation of dilution water: Dilution water was prepared from tap water (Yokohama, in Japan) which was dechlorinated and treated by activated carbon and, the water was aerated enough. - Intervals of water quality measurement: Water chemistry and temperature were measured for each concentration every day (both before and after water change).   OTHER TEST CONDITIONS - Photoperiod: 16:8 hours, light-darkness cycle.   TEST CONCENTRATIONS - Test concentrations: Control and 100 mg/L (limit test). |

***Reference substance (positive control)***

|  |
| --- |
| yes (copper sulfate pentahydrate) |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 96 h | LC50 | > 100 mg/L | nominal |  | mortality |  |

***Details on results***

|  |
| --- |
| - Behavioural abnormalities: No symptoms were observed in control and 100 mg/L. |

***Results with reference substance (positive control)***

|  |
| --- |
| - LC50: (96hr) 0.74 mg/L. |

***Reported statistics and error estimates***

|  |
| --- |
| Because of the limiting test, the LC50 values were not calculated, and were presented more than the highest concentration. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Measured Concentrations: The test concentrations were measured at the start and 24th-hour (old solution before water change) during test exposure using GC.  Table1. Concentration of the Test Substance in Test Water.   |  |  |  |  | | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Concentration, mg/L | | Geometric  Mean  (mg/L) | | (Percent of Nominal) | | | 0 hr (new) | 24 hr (old) | | Control | <0.2 | <0.2 | --- | | 100 | 97.2 (97) | 82.3 (82) | 89.4 (89) |   -Effect Data (mortality):  LC50 (96hr) >100 mg/L (nc)  LC0 (96hr) 100 mg/L (nc)  nc: based on nominal concentrations  Toxic values were calculated by nominal concentrations, because measured concentrations were not deviated over than +/- 20% of nominal.  - Cumulative Mortality: No individuals were killed during exposure period at both control and 100 mg/L.  Table2. The Cumulative Numbers of Dead Oryzias latipes (Percent Mortality).   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured  Conc. (mg/L) | Cumulative Number of Dead | | | | | (Percent Mortality) | | | | | 24 hour | 48 hour | 72 hour | 96 hour | | Control | --- | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | 100 | 89.4 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |

***Endpoint study record: MOE\_Prologed toxicity to fish.002***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-581770bd-9d8b-408e-b1b3-67b83663c1e0 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-22 14:22:18 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MOE, Japan | 1998 | Ecotoxicity of 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- for aquatic species of algae, daphnia and fish. | Unpublished |  |  |  |  |  |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 204 (Fish, Prolonged Toxicity Test: 14-day Study) |  |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material: 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- - Purity: 97.1% - Lot/batch No.: LEM0646 (Wako Pure Chemical Industries, Ltd.)  - Stability under test conditions: IR absorption spectrum of the chemical was taken at the start and the end of the test, and both spectrums were not contradictory to each other.  - Storage condition of test material: Stored in a refrigerator. |

**Analytical monitoring**

|  |
| --- |
| yes |

***Details on sampling***

|  |
| --- |
| - Concentrations: All concentrations were measured at the start, 7th-day after starting the test and the end of the test. |

***Details on analytical methods***

|  |
| --- |
| IDENTIFICATION AND QUANTIFICATION OF TEST SUBSTANCE/PRODUCT - Separation method (e.g. HPLC, GC): GC |

**Vehicle**

|  |
| --- |
| no |

***Details on test solutions***

|  |
| --- |
| PREPARATION AND APPLICATION OF TEST SOLUTION (especially for difficult test substances) - Method: Stock solution (concentration of 45000 mg/L) was prepared by diluting the test chemical with pure water. |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| Oryzias latipes |

***Details on test organisms***

|  |
| --- |
| TEST ORGANISM - Source: Obtained from private fish farm in Japan.  - Length at study initiation (length definition, mean, range and SD): 1.82 cm (1.58 - 2.15 cm, n=10).  - Weight at study initiation (mean and range, SD): 0.114 g (0.073 - 0.164 g, n=10).   - Food type: Commercial TETRAMIN.  - Amount: The rate of 2% of fish weight.  - Frequency: Every day.   ACCLIMATION - Acclimation period: 19 days before testing.  - Acclimation conditions (same as test or not): Same as test. - Type and amount of food: TETRAMIN.  - Feeding frequency: Starved for 24 hours before the test started.  - Health during acclimation (any mortality observed): The mortality of the test organisms for 7 days before testing was below 5 %. |

**Study design**

**Test type**

|  |
| --- |
| flow-through |

**Water media type**

|  |
| --- |
| freshwater |

**Limit test**

|  |
| --- |
| yes |

**Total exposure duration**

|  |
| --- |
| 14 d |

**Test conditions**

***Hardness***

|  |
| --- |
| 63 mg/L (as CaCO3) (dilution water). |

***Test temperature***

|  |
| --- |
| 24 +/- 1 C (setting).  24.0 - 24.5 C (during test period). |

***pH***

|  |
| --- |
| 7.8 (dilution water).  7.3 - 7.9 (during test period). |

***Dissolved oxygen***

|  |
| --- |
| 7.5 - 8.7 mg/L (more than 60% of saturation) (during test period) |

***Nominal and measured concentrations***

|  |
| --- |
| Nominal concentrations: control and 99.8 mg/L (limit test).  Mean measured concentrations: 89.0 mg/L. |

***Details on test conditions***

|  |
| --- |
| TEST SYSTEM - Test vessel: 5.0 L glass beaker (18cm in diameter, 22 cm in depth, ca. 12cm in water depth) with a Teflon sheet on water surface.  - Aeration: None  - Renewal rate of test solution (frequency/flow rate): ca. 32 L/day (22.55 ml/min)  - No. of organisms per vessel:10 - No. of vessels per concentration (replicates):1 - No. of vessels per control (replicates):1  TEST MEDIUM / WATER PARAMETERS - Source/preparation of dilution water: : Dilution water was prepared from tap water (Yokohama, in Japan) which was dechlorinated and treated by activated carbon, and the water was aerated enough. - Intervals of water quality measurement: Water chemistry and temperature were measured for each concentration three times a week.   OTHER TEST CONDITIONS - Photoperiod: 16:8 hours, light-darkness cycle   TEST CONCENTRATIONS - Test concentrations: control and 99.8 mg/L (limit test). |

***Reference substance (positive control)***

|  |
| --- |
| yes (copper sulfate pentahydrate) |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 14 d | LC50 | > 99.8 mg/L | nominal |  | mortality |  |
| 14 d | NOEC | > 99.8 mg/L | nominal |  | other: mortality, growth, symptom |  |

***Details on results***

|  |
| --- |
| - Behavioural abnormalities: No symptoms were observed in control and 99.8 mg/L.  - Observations on body length and weight: No significant difference was detected in 99.8 mg/L compared to control in fish weight and length at the end of the test.  - Mortality of control: None. - Other adverse effects control: None. |

***Results with reference substance (positive control)***

|  |
| --- |
| - LC50: (96hr) 0.73 mg/L. |

***Reported statistics and error estimates***

|  |
| --- |
| Because of the limiting test, the LC50 values were not calculated, and were presented more than the highest concentration. NOEC value (growth) was determined by Dunnett’s multiple comparison. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Measured Concentrations: The test concentrations were measured at the start, 7th-day after starting the test and the end of the test using GC.  Table1. Concentration of the Test Substance in Test Water.   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Concentration, mg/L | | | Mean Measured Conc.  (mg/L) | | (Percent of Nominal) | | | | 0 Day | 7 Day | 14 Day | | Control | <0.2 | <0.2 | <0.2 | --- | | 99.8 | 93.5 (94) | 85.4 (86) | 88.2 (88) | 89.0 (89) |   Toxic values were calculated by nominal concentrations, because measured concentration percentages of nominal concentration kept the variation within +/- 20%.  -Effect Data (mortality):  LC50 (14day) >99.8 mg/L (nc)  LC0 (14day) 99.8 mg/L (nc)  nc: based on nominal concentrations  -Effect Data (toxicological symptom):  NOEC (14day) 99.8 mg/L (nc)  - Cumulative Mortality: No mortality was observed for 14 days at both control and 99.8 mg/L.  Table2. The Cumulative Numbers of Dead Oryzias latipes (Percent Mortality).   |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured  Conc. (mg/L) | Cumulative Number of Dead | | | | | | | (Percent Mortality) | | | | | | | 2 days | 4 days | 7 days | 9 days | 11 days | 14 days | | Control | --- | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | 99.8 | 89.0 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |

***Endpoint study record: QSAR Toolbox\_Fish***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-1aaec733-b091-45da-94ea-e6522ad21b42 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-07-04 10:14:16 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study result type** | read-across based on grouping of substances (category approach) |  |  |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
|  |  | 2011 | QSAR Toolbox 2.1.2.865 prediction for LC50 trend analysis evaluation for 77-85-0 | http://www.oecd.org/ |  |  |  |  |  |

**Materials and methods**

**GLP compliance**

|  |
| --- |
| no data |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| SMILES:C(C)(CO)(CO)CO |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| other: Oryzias latipes;Lepomis macrochirus;Pimephales promelas;Oncorhynchus mykiss;Poecilia reticulata;Leuciscus idus;Menidia beryllina;Morone saxatilis;Carassius auratus;Gambusia affinis;Alburnus alburnus;Cyprinodon variegatus;Agonus cataphractus;Ictalurus punc |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 4 | LC50 | 10400 mg/L |  |  |  |  |

***Details on results***

|  |
| --- |
| 96h LC50: 10364.44 mg/L |

**Any other information on results incl. tables**

|  |
| --- |
| **The prediction was based on dataset comprised from the following descriptors: LC50 Estimation method: Linear approximation Model equation: LC50 = +1.31 (±0.14) +0.816 (±0.046) \* log Kow, log(1/mol/L) Domain logical expression:Result: In Domain** (((((("a" and "b")and("c" and(not "d")))and("e" and(not "f")))and("g" and(not "h")))and("i" and(not "j")))and("k" and "l"))  **Domain logical expression index: "a"** *Referential boundary:*The target chemical should be classified as Neutral Organics by Aquatic toxicity classification by ECOSAR  **Domain logical expression index: "b"** *Referential boundary:*The target chemical should be classified as Discrete chemical by Substance Type  **Domain logical expression index: "c"** *Referential boundary:*The target chemical should be classified as Non-Metals by Groups of elements  **Domain logical expression index: "d"** *Referential boundary:*The target chemical should be classified as Alkali Earth OR Halogens OR Metalloids OR Metals OR Rare Earth OR Transition Metals by Groups of elements  **Domain logical expression index: "e"** *Referential boundary:*The target chemical should be classified as Basesurface narcotics by Acute aquatic toxicity MOA by OASIS  **Domain logical expression index: "f"** *Referential boundary:*The target chemical should be classified as Reactive unspecified by Acute aquatic toxicity MOA by OASIS  **Domain logical expression index: "g"** *Referential boundary:*The target chemical should be classified as No binding by DNA binding by OASIS  **Domain logical expression index: "h"** *Referential boundary:*The target chemical should be classified as Nitro compounds OR Polycyclic Aromatic Hydrocarbons (PAHs) by DNA binding by OASIS  **Domain logical expression index: "i"** *Referential boundary:*The target chemical should be classified as Low (Class I) by Toxic hazard classification by Cramer (with extensions)  **Domain logical expression index: "j"** *Referential boundary:*The target chemical should be classified as High (Class III) OR Intermediate (Class II) by Toxic hazard classification by Cramer (with extensions)  **Domain logical expression index: "k"** *Parametric boundary:*The target chemical should have a value of log Kow which is >= -1.48  **Domain logical expression index: "l"** *Parametric boundary:*The target chemical should have a value of log Kow which is <= 5.27 |

**Overall remarks, attachments**

**Overall remarks**

|  |
| --- |
|  |

**Attached background material**

|  |  |
| --- | --- |
| **Attached document** | **Remarks** |
| Prediction report [7D85589F-C9DE-45C0-B09C-1350BCA1EEAC]1.pdf (application/pdf) | Toolbox generated report |

**Applicant's summary and conclusion**

**Executive summary**

|  |
| --- |
|  |

**6.1.3 Short-term toxicity to aquatic invertebrates**

***Endpoint study record: MOE\_Acute toxicity to Daphnia magna.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-28946861-9cce-437e-8f57-f6c70fa798d8 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-22 14:08:46 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MOE, Japan | 1998 | Ecotoxicity of 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- for aquatic species of algae, daphnia and fish. | Unpublished |  |  |  |  |  |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) |  |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material: 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- - Purity: 97.1%  - Lot/batch No.: LEM0646 (Wako Pure Chemical Industries, Ltd.) - Stability: IR absorption spectrum of the chemical was taken at the start and the end of the test, and both spectrums were not contradictory to each other. - Storage condition of test material: Stored in a refrigerator. |

**Analytical monitoring**

|  |
| --- |
| yes |

***Details on sampling***

|  |
| --- |
| - Concentrations: All concentrations were measured at the start and the end of the test. |

***Details on analytical methods***

|  |
| --- |
| IDENTIFICATION AND QUANTIFICATION OF TEST SUBSTANCE/PRODUCT - Separation method (e.g. HPLC, GC): GC |

**Vehicle**

|  |
| --- |
| no |

***Details on test solutions***

|  |
| --- |
| PREPARATION AND APPLICATION OF TEST SOLUTION (especially for difficult test substances) - Method: Test solution (concentration of 1000 mg/L) was prepared by diluting the test chemical with dilution water. |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| Daphnia magna |

***Details on test organisms***

|  |
| --- |
| TEST ORGANISM - Source: Obtained from National Institute for Environmental Studies in Japan and had been reproduced in testing laboratory. - Age at study initiation (mean and range, SD): < 24 hours old.   - Feeding during test: None  ACCLIMATION - Acclimation period: for 3 weeks - Acclimation conditions (same as test or not): same as test  - Type and amount of food: Chlorella vulgaris  - Feeding frequency: 0.15 mg carbon/day/individual  - Health during acclimation (any mortality observed): During acclimatization, mortality of parental daphnia was below 10% and resting eggs and males were not shown. |

**Study design**

**Test type**

|  |
| --- |
| static |

**Water media type**

|  |
| --- |
| freshwater |

**Limit test**

|  |
| --- |
| yes |

**Total exposure duration**

|  |
| --- |
| 48 h |

**Test conditions**

***Hardness***

|  |
| --- |
| 63 mg/L as CaCO3 (dilution water) |

***Test temperature***

|  |
| --- |
| 20+/-1C (setting).  19.4 - 19.6 C (during test period). |

***pH***

|  |
| --- |
| 8.1 (dilution water).  7.6 - 7.9 (during test period). |

***Dissolved oxygen***

|  |
| --- |
| 8.4 - 8.6 mg/L (during test period). |

***Nominal and measured concentrations***

|  |
| --- |
| Nominal concentrations: control, and 1000 mg/L (1000 mg/L is the highest concentration which can prepare the test solution. Limit test) |

***Details on test conditions***

|  |
| --- |
| TEST SYSTEM - Test vessel: 100 mL test solution in a 100 mL-glass beaker.  - No. of organisms per vessel: 5  - No. of vessels per concentration (replicates): 4  - No. of vessels per control (replicates): 4   TEST MEDIUM / WATER PARAMETERS - Source/preparation of dilution water: Dilution water was prepared from tap water (Yokohama, in Japan) which was dechlorinated and treated by activated carbon. Before use, the water was aerated enough.  - Intervals of water quality measurement: Water chemistry and temperature were measured for control and 1000 mg/L at the start and the end of the test.  OTHER TEST CONDITIONS - Photoperiod: 16:8 hours, light-darkness cycle  - Light intensity: =< 1200 lux   TEST CONCENTRATIONS - Test concentrations: control and 1000 mg/L (1000 mg/L is the highest concentration which can prepare the test solution. Limit test) |

***Reference substance (positive control)***

|  |
| --- |
| yes (potassium dichromate) |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 48 h | EC50 | > 1000 mg/L | nominal |  | mortality |  |

***Details on results***

|  |
| --- |
| - Mortality of control: 0% - Other adverse effects control: None. |

***Results with reference substance***

|  |
| --- |
| - EC50 (48hr, immobility) was 0.23 mg/L. |

***Reported statistics and error estimates***

|  |
| --- |
| Because of the limiting test, the EC50 values were not calculated, and were presented more than the highest concentration. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Measured Concentrations: The test concentrations were measured at the start and the end of the test using GC.  Table1. Measured Concentration of the Test Substance in Test Water.   |  |  |  | | --- | --- | --- | | Nominal Conc.  (mg/L) | Measured Concentration (mg/L)  (Percent of Nominal, %) | | | 0 hr (new) | 48 hr (old) | | Control | ＜0.2 | ＜0.2 | | 1000 | 945 (95) | 991 (99) |   Toxic values were calculated by nominal concentrations, because measured concentration percentages of nominal concentration kept the variation within +/- 20 %.  -Effect Data:  EC50 (48hr) >1000 mg/L (nc)  nc: based on nominal concentrations.  -Mortality or Immobility: None of test organisms were immobilized the behaviours at both control and 1000 mg/L.  Table2. The Numbers of Immobile Daphnia magna (Percent Immobility).   |  |  |  | | --- | --- | --- | | Nominal Conc.(mg/L) | Cumulative Number of Immobilized Daphnia (Percent Immobility, %) | | | 24 hr | 48 hr | | Control | 0 (0) | 0 (0) | | 1000 | 0 (0) | 0 (0) | |

***Endpoint study record: QSAR Toolbox\_Daphnia***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-66ac1857-cf2a-473c-a66e-8c76fceeafed |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-07-04 10:15:38 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study result type** | read-across based on grouping of substances (category approach) |  |  |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
|  |  | 2011 | QSAR Toolbox 2.1.2.865 prediction for EC50,LC50 trend analysis evaluation for 77-85-0 | http://www.oecd.org/ |  |  |  |  |  |

**Materials and methods**

**GLP compliance**

|  |
| --- |
| no data |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| SMILES:C(C)(CO)(CO)CO |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| Daphnia magna |

**Study design**

**Total exposure duration**

|  |
| --- |
| 2 |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 48 h | other: EC50,LC50 | 6770 mg/L |  |  |  |  |

***Details on results***

|  |
| --- |
| EC50, LC50: 6771.521 mg/L |

**Any other information on results incl. tables**

|  |
| --- |
| **The prediction was based on dataset comprised from the following descriptors: EC50,LC50 Estimation method: Linear approximation Model equation: EC50,LC50 = +1.51 (±0.27) +0.875 (±0.073) \* log Kow, log(1/mol/L) Domain logical expression:Result: In Domain** ((((("a" and "b")and("c" and(not "d")))and("e" and(not "f")))and("g" and(not "h")))and("i" and "j"))  **Domain logical expression index: "a"** *Referential boundary:*The target chemical should be classified as Neutral Organics by Aquatic toxicity classification by ECOSAR  **Domain logical expression index: "b"** *Referential boundary:*The target chemical should be classified as Discrete chemical by Substance Type  **Domain logical expression index: "c"** *Referential boundary:*The target chemical should be classified as Non-Metals by Groups of elements  **Domain logical expression index: "d"** *Referential boundary:*The target chemical should be classified as Alkali Earth OR Halogens OR Metalloids OR Metals OR Transition Metals by Groups of elements  **Domain logical expression index: "e"** *Referential boundary:*The target chemical should be classified as Basesurface narcotics by Acute aquatic toxicity MOA by OASIS  **Domain logical expression index: "f"** *Referential boundary:*The target chemical should be classified as Reactive unspecified by Acute aquatic toxicity MOA by OASIS  **Domain logical expression index: "g"** *Referential boundary:*The target chemical should be classified as Group 14 - Carbon C AND Group 16 - Oxygen O by Chemical elements  **Domain logical expression index: "h"** *Referential boundary:*The target chemical should be classified as Group 15 - Nitrogen N OR Group 16 - Sulfur S by Chemical elements  **Domain logical expression index: "i"** *Parametric boundary:*The target chemical should have a value of log Kow which is >= -1.76  **Domain logical expression index: "j"** *Parametric boundary:*The target chemical should have a value of log Kow which is <= 6.09 |

**Overall remarks, attachments**

**Overall remarks**

|  |
| --- |
|  |

**Attached background material**

|  |  |
| --- | --- |
| **Attached document** | **Remarks** |
| Prediction report [E23A0E9B-D2B5-418D-B97B-66A8592D2F15]1.pdf (application/pdf) | Toolbox generated report |

**Applicant's summary and conclusion**

**Executive summary**

|  |
| --- |
|  |

**6.1.4 Long-term toxicity to aquatic invertebrates**

***Endpoint study record: MOE\_Chronic toxicity to Daphnia magna.002***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-8064c2d6-6357-4f4d-a8be-e1eb246822b5 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-07-05 15:31:50 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MOE, Japan | 1998 | Ecotoxicity of 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- for aquatic species of algae, daphnia and fish. | Unpublished |  |  |  |  |  |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 211 (Daphnia magna Reproduction Test) |  |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material : 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- - Purity: 97.1 %  - Lot/batch No.: LEM0646 (Wako Pure Chemical Industries, Ltd.)   - Stability: IR absorption spectrum of the chemical was taken at the start and the end of the test, and both spectrums were not contradictory to each other.  - Storage condition of test material: Stored in a refrigerator. |

**Analytical monitoring**

|  |
| --- |
| yes |

***Details on sampling***

|  |
| --- |
| - Concentrations: All concentrations were measured 4 sets during test period. 1 set of measurement consists of both new preparing solution and old solution after 2 or 3 days exposure. |

***Details on analytical methods***

|  |
| --- |
| IDENTIFICATION AND QUANTIFICATION OF TEST SUBSTANCE/PRODUCT - Separation method (e.g. HPLC, GC): GC |

**Vehicle**

|  |
| --- |
| no |

***Details on test solutions***

|  |
| --- |
| PREPARATION AND APPLICATION OF TEST SOLUTION (especially for difficult test substances) - Method: Stock solution (concentration of 5000 mg/L) was prepared by diluting the test chemical with pure water. |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| Daphnia magna |

***Details on test organisms***

|  |
| --- |
| TEST ORGANISM - Source: Obtained from National Institute for Environmental Studies in Japan and had been reproduced in testing laboratory. - Age of parental stock (mean and range, SD): < 24 hours old  - Feeding during test - Food type: Green algae (Chlorella vulgaris)  - Amount: 0.1-0.2 mgC/day/individual.   ACCLIMATION - Acclimation period: for 2 weeks. - Acclimation conditions (same as test or not): same as test  - Type and amount of food: Chlorella vulgaris  - Feeding frequency: 0.15 mg carbon/day/individual  - Health during acclimation (any mortality observed): During acclimatization, mortality of parental daphnia was 0% and resting eggs and males were not shown. |

**Study design**

**Test type**

|  |
| --- |
| semi-static |

**Water media type**

|  |
| --- |
| freshwater |

**Limit test**

|  |
| --- |
| yes |

**Total exposure duration**

|  |
| --- |
| 21 d |

**Test conditions**

***Hardness***

|  |
| --- |
| 63 mg/L as CaCO3 (dilution water).  65-85 mg/L as CaCO3 (during test period). |

***Test temperature***

|  |
| --- |
| 20 +/- 1 C (setting).  19.7 - 20.5 C (during test period). |

***pH***

|  |
| --- |
| 8.1 (dilution water).  7.5 - 7.9 (during test period). |

***Dissolved oxygen***

|  |
| --- |
| 7.7 - 8.9 mg/L (more than 60% of saturation) (during test period). |

***Nominal and measured concentrations***

|  |
| --- |
| Nominal concentrations: control and 100 mg/L (limit test).  Measured concentrations: control and 88.5 mg/L (time-weighted mean). |

***Details on test conditions***

|  |
| --- |
| TEST SYSTEM - Test vessel: 80 mL test solution in a 100 mL-glass beaker.  - Renewal rate of test solution (frequency/flow rate): Three times per a week.  - No. of organisms per vessel: 10  - No. of vessels per concentration (replicates): 1  - No. of vessels per control (replicates): 1   TEST MEDIUM / WATER PARAMETERS - Source/preparation of dilution water: Dilution water was prepared from tap water (Yokohama, in Japan) which was dechlorinated and treated by activated carbon. Before use, the water was aerated enough.   - Intervals of water quality measurement: Water chemistry and temperature were measured for control and 100 mg/L at 0, 2, 7, 9 (both old and new solution), 12, 19, and 21st-day.   OTHER TEST CONDITIONS - Photoperiod: 16:8 hours, light - darkness cycle. - Light intensity: =< 1200 lux. |

***Reference substance (positive control)***

|  |
| --- |
| yes (potassium dichromate) |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 21 d | NOEC | > 88.5 mg/L | meas. (TWA) |  | reproduction |  |

***Results with reference substance (positive control)***

|  |
| --- |
| - EC50 (48hr, immobility): 0.23 mg/L |

***Reported statistics and error estimates***

|  |
| --- |
| LC50 and EC50: Because of the limiting test, the E/LC50 values were not calculated, and were presented more than the highest concentration.  NOEC: The cumulative number of juveniles produced per adult in control and 100 mg/L after 21days were tested by F-test and Student’s t-test. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Measured Concentrations: The test concentrations were measured 4 times (both before and after water replacement) using GC.  Table1. Measured Concentration of Test Substance in Test Water during a 21-day Exposure Period.   |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Concentration (mg/L) | | | | | | | | Times-weighted mean\* | | 0 | 2 | 7 | 9 | 9 | 12 | 19 | 21 | | new | old | new | old | new | old | new | old | | Control | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | <0.2 | -- | | 100 | 103 | 87.6 | 79.1 | 77.6 | 93.1 | 88.7 | 94.2 | 79.5 | 88.5 |   \*: Time-weighted mean as defined in OECD TG 211.  new: freshly prepared test solution.  old: old test solution before renewal.  -Effect Data (Parental Mortality):  LC50 (21days): >88.5 mg/L (mc).  -Effect Data (Reproduction):  EC50 (21days): >88.5 mg/L (mc).  NOEC (21days): >88.5 mg/L (mc).  mc: based on measured concentrations.  - Cumulative Number of Died Parental Daphnia:  Table2. Mortality (%) of Parental Daphnia.   |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Conc. (mg/L) | Mortality (%) | | | | | | | Days | | | | | | | 1 | 2 | 4 | 7 | 14 | 21 | | Control | --- | 0 | 0 | 0 | 0 | 10 | 20 | | 100 | 88.5 | 0 | 0 | 0 | 0 | 10 | 20 |   -Time (days) to First Brood Production.  : 7 - 8 days (both control and 100 mg/L)  -Cumulative numbers of juveniles produced per adult alive.  Table3. Mean Cumulative Numbers of Offspring Produced per Adult Alive for 21 Days   |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Conc. (mg/L) | Mean Cumulative Numbers of Juveniles Produced Per Adult Alive for 21 days | | | | | | | | | |  | | Days | | | | | | | | |  | | 0---6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |  | | Control | --- | 0---0 | 7.3 | 11.4 | 11.4 | 28.9 | 39.4 | 39.4 | 54 | 61.9 |  | | 100 | 88.5 | 0---0 | 5.4 | 14 | 14.4 | 28.3 | 43.8 | 43.8 | 58 | 68.1 |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Conc. (mg/L) | Mean Cumulative Numbers of Juveniles Produced Per Adult Alive for 21 days | | | | | | | |  | | Days | | | | | | |  | | 15 | 16 | 17 | 18 | 19 | 20 | 21 |  | | Control | --- | 61.9 | 82.6 | 95.3 | 95.3 | 104.4 | 115.4 | 115.6 |  | | 100 | 88.5 | 68.1 | 81.9 | 92.3 | 95.1 | 104.9 | 109.1 | 109.1 |  |   -Cumulative numbers of juveniles produced per adult alive for 21 days.  Table4. Cumulative numbers of offspring produced per adult alive for 21 days in each test vessel.   |  |  |  | | --- | --- | --- | | Vessel No. | Measured Concentration (mg/L) | | | Control | 88.5 | | 1 | 109 | 105 | | 2 | 110 | 103 | | 3 | 103 | 110 | | 4 | D | D | | 5 | 123 | 109 | | 6 | D | 120 | | 7 | 113 | 136 | | 8 | 127 | D | | 9 | 125 | 102 | | 10 | 115 | 88 | | Mean | 115.6 | 109.1 | | S.D. | 8.6 | 14.1 | | Inhibition rate (%) | - | 5.6 | | Significant difference | - | - |   D: were not included for calculation because the parental Daphnia was dead during the 21-day test period.  -: Indicates no significant difference. |

**6.1.5 Toxicity to aquatic algae and cyanobacteria**

***Endpoint study record: MOE\_Toxicity to aquatic algae.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-e1edd4fb-c462-433b-8de7-8ad572df47f0 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-29 18:49:08 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MOE, Japan | 1998 | Ecotoxicity of 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- for aquatic species of algae, daphnia and fish. | Unpublished |  |  |  |  |  |

**Materials and methods**

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 201 (Alga, Growth Inhibition Test) |  |

**GLP compliance**

|  |
| --- |
| yes (incl. certificate) |

**Test materials**

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material: 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl-  - Purity: 97.1%  - Lot/batch No.: LEM0646 (Wako Pure Chemical Industries, Ltd.)   - Stability: IR absorption spectrum of the chemical was taken at the start and the end of the test, and both spectrums were not contradictory to each other.  - Storage condition of test material: Stored in a refrigerator. |

**Analytical monitoring**

|  |
| --- |
| yes |

***Details on sampling***

|  |
| --- |
| - Concentrations: All test concentrations were measured at the start and the end of test. |

***Details on analytical methods***

|  |
| --- |
| IDENTIFICATION AND QUANTIFICATION OF TEST SUBSTANCE/PRODUCT - Separation method (e.g. HPLC, GC): GC |

**Vehicle**

|  |
| --- |
| no |

***Details on test solutions***

|  |
| --- |
| PREPARATION AND APPLICATION OF TEST SOLUTION (especially for difficult test substances) - Method: Stock solution of concentration 20,000 mg/L was prepared by dissolving the test chemical in test medium. |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| other: Pseudokirchneriella subcapitata |

***Details on test organisms***

|  |
| --- |
| TEST ORGANISM - Strain: ATCC22662.  - Source (laboratory, culture collection): Obtained from American Type Culture Collection and cultivated aseptically in laboratory.  - Method of cultivation: Sterile.  ACCLIMATION - Acclimation period: for 4 days.  - Culturing media and conditions (same as test or not): same methods of the test in OECD medium. |

**Study design**

**Test type**

|  |
| --- |
| static |

**Water media type**

|  |
| --- |
| freshwater |

**Limit test**

|  |
| --- |
| yes |

**Total exposure duration**

|  |
| --- |
| 72 h |

**Test conditions**

***Test temperature***

|  |
| --- |
| 23 +/- 2 C (setting), 23.0 – 23.3 C (during test period) |

***pH***

|  |
| --- |
| 7.8 - 10.1 (all test period), 7.8 - 7.9 (0 h), 10.0 - 10.1 (72 h) |

***Nominal and measured concentrations***

|  |
| --- |
| Nominal Concentrations: control and 1000 mg/L (limit test). |

***Details on test conditions***

|  |
| --- |
| TEST SYSTEM - Test vessel: 100 mL medium in a 300mL glass Erlenmeyer flask with breathable silicon cap.  - Type (delete if not applicable): open  - Initial cells density: 10,000 cells/mL. - No. of vessels per concentration (replicates): 3  - No. of vessels per control (replicates): 3   GROWTH MEDIUM - Standard medium used: yes  TEST MEDIUM / WATER PARAMETERS - Source/preparation of dilution water: OECD medium.   OTHER TEST CONDITIONS - Sterile test conditions: yes - Photoperiod: Continuously  - Light intensity and quality: 4000 - 5000 lux.   EFFECT PARAMETERS MEASURED (with observation intervals if applicable) : - Determination of cell concentrations: [electronic particle counter]  TEST CONCENTRATIONS - Test concentrations: control and 1000 mg/L (limit test). |

***Reference substance (positive control)***

|  |
| --- |
| yes (potassium dichromate) |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 72 h | EC50 | > 1000 mg/L | nominal |  | growth rate |  |
| 72 h | EC50 | > 1000 mg/L | nominal |  | other: area under growth curve |  |
| 72 h | NOEC | > 1000 mg/L | nominal |  | growth rate |  |
| 72 h | NOEC | > 1000 mg/L | nominal |  | other: area under growth curve |  |

***Results with reference substance (positive control)***

|  |
| --- |
| - EbC50 (0-72hr): 0.41 mg/L. |

***Reported statistics and error estimates***

|  |
| --- |
| Parametric Dunnett's test (a=0.05) for NOEC. Because of the limiting test, the EC50 values were not calculated, and were presented more than the highest concentration. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Measured Concentrations: Test concentrations were measured at the start and the end of test using by GC.  Table1. Concentration of the Test Substance in Test Water.   |  |  |  | | --- | --- | --- | | Nominal Conc. (mg/L) | Measured Concentration (mg/L)  (Percent of Nominal, %) | | | 0 hour (new) | 72 hours (old) | |  | | Control | <0.2 | <0.2 |  | | 1000 | 937 (94) | 991 (99) |  |   Table2. pH Values   |  |  |  | | --- | --- | --- | | Nominal Conc. (mg/L) | pH | | | 0hour | 72hour | | Control | 7.9 | 10 | | 1000 | 7.8 | 10.1 |   -Effect Data (rate method):  EC50 (0 - 72 hr): > 1,000 mg/L (nc).  NOEC (0 - 72 hr): > 1,000 mg/L (nc).  nc: based on nominal concentration.  -Effect Data (area method; area under growth curve):  EC50 > 1,000 mg/L (nc).  NOEC (0 - 72 hr): > 1,000 mg/L (nc).  - Growth Inhibition (%) of Pseudokirchneriella subcapitata.  Table3. Growth Rate, Inhibition and Cell density of Pseudokirchneriella subcapitata.   |  |  |  |  | | --- | --- | --- | --- | | Nominal Conc. (mg/L) | Growth Rate, Inhibition and Cell density | | | | Rate (Average) | Inhibition (%) | Cell density (cells/ml) | | u(0-72hr) | Iu (0-72hr) | (72hr) | | Control | 1.87 | - | 2,769,600 | | 1000 | 1.86 | 1.99 | 2,689,600 |   - Growth Curves: Exponential growth phase during 72 hours.  Measurement of algal biomass was not conducted in this test. Present values were obtained and estimated by growth rate based on number of algal cells. |

***Endpoint study record: QSAR Toolbox\_Algae***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-8274d2dd-1653-4885-98cb-9bef95015380 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-07-04 10:23:18 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study result type** | read-across based on grouping of substances (category approach) |  |  |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
|  |  | 2011 | QSAR Toolbox 2.1.2.865 prediction for EC50 trend analysis evaluation for 77-85-0 | http://www.oecd.org/ |  |  |  |  |  |

**Materials and methods**

**GLP compliance**

|  |
| --- |
| no data |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| SMILES:C(C)(CO)(CO)CO |

**Test organisms**

**Test organisms (species)**

|  |
| --- |
| other: Pseudokirchneriella subcapitata |

**Study design**

**Total exposure duration**

|  |
| --- |
| 3 |

**Results and discussions**

**Effect concentrations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Duration** | **Endpoint** | **Effect conc.** | **Nominal/Measured** | **Conc. based on** | **Basis for effect** | **Remarks (e.g. 95% CL)** |
| 72 h | EC50 | 75 mg/L |  |  |  |  |

***Details on results***

|  |
| --- |
| EC50: 74.95972 mg/L |

**Any other information on results incl. tables**

|  |
| --- |
| **The prediction was based on dataset comprised from the following descriptors: EC50 Estimation method: Linear approximation Model equation: EC50 = +3.34 (±1.04) +0.432 (±0.309) \* log Kow, log(1/mol/L) Domain logical expression:Result: In Domain** (((((("a" and "b")and("c" and(not "d")))and("e" and(not "f")))and("g" and(not "h")))and("i" and(not "j")))and("k" and "l"))  **Domain logical expression index: "a"** *Referential boundary:*The target chemical should be classified as Neutral Organics by Aquatic toxicity classification by ECOSAR  **Domain logical expression index: "b"** *Referential boundary:*The target chemical should be classified as Discrete chemical by Substance Type  **Domain logical expression index: "c"** *Referential boundary:*The target chemical should be classified as Non-Metals by Groups of elements  **Domain logical expression index: "d"** *Referential boundary:*The target chemical should be classified as Halogens by Groups of elements  **Domain logical expression index: "e"** *Referential boundary:*The target chemical should be classified as Neutral Organics by Aquatic toxicity classification by ECOSAR  **Domain logical expression index: "f"** *Referential boundary:*The target chemical should be classified as Acid moiety by Aquatic toxicity classification by ECOSAR  **Domain logical expression index: "g"** *Referential boundary:*The target chemical should be classified as Alcohol AND Hydroxy compound AND Primary alcohol by Organic functional groups, Norbert Haider (checkmol)  **Domain logical expression index: "h"** *Referential boundary:*The target chemical should be classified as (N/A) OR Aromatic compound by Organic functional groups, Norbert Haider (checkmol)  **Domain logical expression index: "i"** *Referential boundary:*The target chemical should be classified as Alcohol AND Hydroxy compound AND Primary alcohol by Organic functional groups, Norbert Haider (checkmol)  **Domain logical expression index: "j"** *Referential boundary:*The target chemical should be classified as Carbonic acid derivative OR Carbonyl compound OR Carboxylic acid derivative OR Dialkylether OR Disulfide OR Ether OR Heterocyclic compound OR Ketone OR Lactone OR Secondary alcohol OR Sulfenic acid derivative OR Sulfone by Organic functional groups, Norbert Haider (checkmol)  **Domain logical expression index: "k"** *Parametric boundary:*The target chemical should have a value of log Kow which is >= -2.65  **Domain logical expression index: "l"** *Parametric boundary:*The target chemical should have a value of log Kow which is <= 5.27 |

**Overall remarks, attachments**

**Overall remarks**

|  |
| --- |
|  |

**Attached background material**

|  |  |
| --- | --- |
| **Attached document** | **Remarks** |
| Prediction report [3B123EFC-CA81-47F2-BD91-16D3E57D06DA]1.pdf (application/pdf) | Toolbox generated report |

**Applicant's summary and conclusion**

**Executive summary**

|  |
| --- |
|  |

**7 Toxicological information**

**7.2 Acute Toxicity**

**7.2.1 Acute toxicity: oral**

***Endpoint study record: Acute toxicity: oral.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-2f9b94ee-ade7-47b0-a56b-814912f7c565 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:03 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | Single Dose Oral Toxicity Test of 1,1,1-Tris(hydroxymethyl)ethane in Rats | Toxicity Testing Reports of Environmental Chemicals, Vol.6, 41-42 | Hatano Research Institute, Food and Drug Safety Center |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Test type**

|  |
| --- |
| standard acute method |

**Limit test**

|  |
| --- |
| yes |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 401 (Acute Oral Toxicity) | no |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: White flake-shaped material - Analytical purity: 99.0% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Test animals**

**Species**

|  |
| --- |
| rat |

**Strain**

|  |
| --- |
| Crj: CD(SD) |

**Sex**

|  |
| --- |
| male/female |

***Details on test animals and environmental conditions***

|  |
| --- |
| TEST ANIMALS - Source: Charles River Japan Inc. - Age at study initiation: 5 weeks old - Weight at study initiation: Males, 99.8 - 108.9 g; females, 85.3 - 93.2 g - Fasting period before study: Approximately 18 hrs - Housing: One animal/cage - Diet (e.g. ad libitum): Ad libitum except fasting period for 18 hrs before administration to 3 hrs after administration  - Water (e.g. ad libitum): Ad libitum - Acclimation period: 6 days  ENVIRONMENTAL CONDITIONS - Temperature (℃): 23.8 - 24.5℃ - Humidity (%): 54 - 69% - Ventilation (per hr): Approximately 15 times/hr - Photoperiod (hrs light / hrs dark): 12 hrs light / 12 hrs dark |

**Administration / exposure**

**Route of administration**

|  |
| --- |
| oral: gavage |

**Vehicle**

|  |
| --- |
| other: Distilled water for injection |

***Details on oral exposure***

|  |
| --- |
| VEHICLE - Concentration in vehicle: 20% - Lot/batch no. (if required): 9510AH produced by Hikari Pharmaceutical Co., Ltd.  MAXIMUM DOSE VOLUME APPLIED: 10ml/kgbw |

**Doses**

|  |
| --- |
| 2000 mg/kg bw |

**No. of animals per sex per dose**

|  |
| --- |
| 5 animals/sex/dose |

**Control animals**

|  |
| --- |
| no |

***Details on study design***

|  |
| --- |
| - Duration of observation period following administration: 14 days - Frequency of observations:  Day 1 (day of administration): time just after administration ~ 1, 2, 3, 4, 5 and 6 hrs after administration After day 2: once a day  - Frequency of weighing: Days 1 (before administration), 2, 4, 8, 11 and 15  - Necropsy of survivors performed: Yes |

***Statistics***

|  |
| --- |
| No |

**Results and discussions**

***Preliminary study (if fixed dose study)***

|  |
| --- |
| A preliminary test was conducted to determine the experimental doses. Rats (3 animals/sex/dose) were singly given 1,1,1-Tris(hydroxymethyl)ethane at 20, 200 and 2000 mg/kg bw by gavage. As a result, no deaths were observed in either sex in any of the treatment groups. |

**Effect levels**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sex** | **Endpoint** | **Effect level** | **Based on** | **95% CL** | **Remarks** |
| male/female | LD50 | > 2000 mg/kg bw |  |  |  |

***Mortality***

|  |
| --- |
| No deaths were observed in any group. |

***Clinical signs***

|  |
| --- |
| No changes related to the test substance were observed in any group. |

***Body weight***

|  |
| --- |
| No changes related to the test substance were observed in any group. |

***Gross pathology***

|  |
| --- |
| No changes related to the test substance were observed in any group. |

***Other findings***

|  |
| --- |
| - Organ weights: No data - Histopathology: No data - Potential target organs: Not identified - Other observations: No data |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| The LD50 value was more than 2000 mg/kg bw for both sexes. |

***Endpoint study record: Acute toxicity: oral.002***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-e33c5aff-0921-40ac-ab59-cd85c2d61960 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:03 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | disregarded study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 4 (not assignable) | | |
| **Rationale for reliability incl. deficiencies** | Documentation insufficient for assessment | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| other company data | E I Du Pont de Nemours & Co. | 1992 | INITIAL SUBMISSION: PRELIMINARY TOXICITY TESTS OF SODIUM NITRILOTRIACETATE, SODIUM TARTRATE, TARTARIC ACID,METHYLTRIMETHYLOLMETHANE, \* WITH COVER LETTER DATED 10/15/92 | Fiche #: OTS0555808 Doc#: 88-920010539 |  |  |  |  | 1947-12-18 |

**Materials and methods**

**Limit test**

|  |
| --- |
| no |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Methyltrimethylolmethane |

**Test animals**

**Species**

|  |
| --- |
| rat |

**Strain**

|  |
| --- |
| no data |

**Sex**

|  |
| --- |
| no data |

***Details on test animals and environmental conditions***

|  |
| --- |
| no data |

**Administration / exposure**

**Route of administration**

|  |
| --- |
| oral: feed |

**Vehicle**

|  |
| --- |
| no data |

***Details on oral exposure***

|  |
| --- |
| no data |

**Doses**

|  |
| --- |
| Rats were fed doses as high as 7590 mg/kg. |

**No. of animals per sex per dose**

|  |
| --- |
| no data |

**Control animals**

|  |
| --- |
| no data |

***Details on study design***

|  |
| --- |
| - Duration of observation period following administration: 8-15 days - Frequency of observations and weighing: No data - Necropsy of survivors performed: yes - Other examinations performed: Clinical signs, body weight, histopathology |

**Results and discussions**

**Effect levels**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sex** | **Endpoint** | **Effect level** | **Based on** | **95% CL** | **Remarks** |
| no data | LD50 | > 7590 mg/kg bw |  |  |  |

***Mortality***

|  |
| --- |
| no data |

***Clinical signs***

|  |
| --- |
| Rats were fed doses as high as 7590 mg/kg. Aside from some discomfort immediately following treatment, they did not show any untoward effects. |

***Body weight***

|  |
| --- |
| No abnormality. |

***Gross pathology***

|  |
| --- |
| No abnormality. |

***Other findings***

|  |
| --- |
| - Histopathology: No abnormality. |

**7.3 Irritation / corrosion**

**7.3.1 Skin irritation / corrosion**

***Endpoint study record: Skin irritation / corrosion.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-bd0f3b5f-3d7d-4968-b407-96bc0eaf2059 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:04 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | disregarded study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 4 (not assignable) | | |
| **Rationale for reliability incl. deficiencies** | Documentation insufficient for assessment | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| other company data | E I Du Pont de Nemours & Co. | 1992 | INITIAL SUBMISSION: PRELIMINARY TOXICITY TESTS OF SODIUM NITRILOTRIACETATE, SODIUM TARTRATE, TARTARIC ACID,METHYLTRIMETHYLOLMETHANE, \* WITH COVER LETTER DATED 10/15/92 | Fiche #: OTS0555808 Doc#: 88-920010539 |  |  |  |  | 1947-12-18 |

**Materials and methods**

**Type of method**

|  |
| --- |
| no data |

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test materials**

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Methyltrimethylolmethane |

**Test animals**

**Species**

|  |
| --- |
| guinea pig |

**Strain**

|  |
| --- |
| no data |

***Details on test animals and environmental conditions***

|  |
| --- |
| no data |

**Test system**

**Type of coverage**

|  |
| --- |
| no data |

**Preparation of test site**

|  |
| --- |
| no data |

**Vehicle**

|  |
| --- |
| no data |

***Amount/concentration applied***

|  |
| --- |
| no data |

**Duration of treatment / exposure**

|  |
| --- |
| no data |

**Observation period**

|  |
| --- |
| no data |

**Number of animals**

|  |
| --- |
| 10 animals |

**Control animals**

|  |
| --- |
| no data |

***Details on study design***

|  |
| --- |
| no data |

**Results and discussions**

***Irritant/corrosive response data***

|  |
| --- |
| Methyltrimethylolmethane is not particularly irritant to the skin in guinea pigs (See Table 1). No further information is available. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1. Results of skin irritation   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | |  |  | Reactions | | | | |  | Number of guinea pigs | + | Sl+ | VSl+ | Negative | | Initial Patch | 10 |  |  | 1 | 9 | | Final Patch | 10 |  |  | 1 | 9 | |

**7.4 Sensitisation**

**7.4.1 Skin sensitisation**

***Endpoint study record: Skin sensitisation.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-26be0dfa-b5a4-47ab-a626-496baf68dca6 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:04 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | disregarded study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 4 (not assignable) | | |
| **Rationale for reliability incl. deficiencies** | Documentation insufficient for assessment | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| other company data | E I Du Pont de Nemours & Co. | 1992 | INITIAL SUBMISSION: PRELIMINARY TOXICITY TESTS OF SODIUM NITRILOTRIACETATE, SODIUM TARTRATE, TARTARIC ACID,METHYLTRIMETHYLOLMETHANE, \* WITH COVER LETTER DATED 10/15/92 | Fiche #: OTS0555808 Doc#: 88-920010539 |  |  |  |  | 1947-12-18 |

**Materials and methods**

**Type of method**

|  |
| --- |
| in vivo |

**Type of study**

|  |
| --- |
| Patch-Test |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): Methyltrimethylolmethane |

**Test animals**

**Species**

|  |
| --- |
| guinea pig |

**Strain**

|  |
| --- |
| no data |

**Sex**

|  |
| --- |
| no data |

***Details on test animals and environmental conditions***

|  |
| --- |
| no data |

**Test system**

**Traditional sensitisation test**

**Vehicle**

|  |
| --- |
| no data |

**Concentration**

|  |
| --- |
| no data |

**No. of animals per dose**

|  |
| --- |
| 10 animals |

***Details on study design (Traditional tests)***

|  |
| --- |
| no data |

***Positive control substance(s)***

|  |
| --- |
| no data |

**Overall remarks, attachments**

**Overall remarks**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Methyltrimethylolmethane does not produce sensitization in guinea pigs. No further information is available.  Table 1. Result of skin reaction   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | |  |  | Reactions | | | | |  | Number of guinea pigs | + | Sl+ | VS+ | Negative | | Initial Patch | 10 |  |  | 1 | 9 | | Final Patch | 10 |  |  | 1 | 9 | |

**7.5 Repeated dose toxicity**

**7.5.1 Repeated dose toxicity: oral**

***Endpoint study record: Repeated dose toxicity: oral.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-0a411a7b-9f89-47e6-823c-62e4dfe629e1 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:04 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,1,1-Tris(hydroxymethyl)ethane by Oral Administration in Rats. | Toxicity Testing Reports of Environmental Chemicals, Vol.6, 43-53 | Hatano Research Institute, Food and Drug Safety Center |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Cross-reference to same study**

|  |
| --- |
| 7.8.1 Toxicity to reproduction: Toxicity to reproduction.001 7.8.2 Developmental toxicity/teratogenicity: Developmental toxicity/teratogenicity.001 |

**Materials and methods**

**Test type**

|  |
| --- |
| combined repeated dose and reproduction / developmental screening |

**Limit test**

|  |
| --- |
| no |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) | yes (haematological and clinical chemistry examination in only males.) |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: White solid - Analytical purity: 99.0% - Impurities (identity and concentrations): bis(2,2-dimethylol propyl)ether:0.1%, bis(2,2-dimethylol)propoxy methane: 0.3%, pentaerythritol: 0.3%, water: 0.14% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Test animals**

**Species**

|  |
| --- |
| rat |

**Strain**

|  |
| --- |
| Crj: CD(SD) |

**Sex**

|  |
| --- |
| male/female |

***Details on test animals and environmental conditions***

|  |
| --- |
| TEST ANIMALS - Source: Charles River Japan, Inc. Hino - Age at study initiation: 8 weeks old - Weight at study initiation: Male: 296.5 - 330.7 g Female: 195.0 - 223.1 g - Housing: Rats were housed individually, except during the acclimation, mating, and nursing periods. From day 14 of pregnancy until the day of sacrifice, individual dams and litters were reared in rat breeding cages with pulp chips as bedding. - Diet: Ad libitum - Water: Ad libitum - Acclimation period: 6 days ENVIRONMENTAL CONDITIONS - Temperature (°C): 24 ± 1 °C - Humidity (%): 50 - 65% - Air changes (per hr): Approximately 15 times/hr - Photoperiod (hrs dark / hrs light): 12 hrs dark / 12 hrs light |

**Administration / exposure**

**Route of administration**

|  |
| --- |
| oral: gavage |

**Vehicle**

|  |
| --- |
| other: Distilled water for injection |

***Details on oral exposure***

|  |
| --- |
| PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in distilled water for injection.  VEHICLE - Justification for use and choice of vehicle: No data - Amount of vehicle (if gavage): 5 ml/kg bw - Lot/batch no. (if required): 9609CA produced by Hikari Pharmaceutical Co., Ltd. Dosing volume: 5 mL/kg Stability (test solutions): At least 8 days.  Storage condition of test solution: Stored in a refrigerator. |

**Analytical verification of doses or concentrations**

|  |
| --- |
| yes |

**Duration of treatment / exposure**

|  |
| --- |
| (P)Males: 42 days including 14 days pre-mating period and the subsequent 28 days (P)Females: Days including 14 days pre-mating, mating and gestation periods and the days until day 3 of lactation (a total of up to 49 days) |

**Frequency of treatment**

|  |
| --- |
| Daily |

**Doses/concentrations**

|  |  |
| --- | --- |
| 0, 100, 300 and 1000 mg/kg bw/day | |
| **Basis** | actual ingested |

**No. of animals per sex per dose**

|  |
| --- |
| 13 animals/sex/dose |

**Control animals**

|  |
| --- |
| yes, concurrent vehicle |

***Details on study design***

|  |
| --- |
| - Dose selection rationale: A preliminary study was conducted to determine the doses to be employed. The substance was administered for 2 weeks. As a result, decrease in body weight was observed in both sexes at doses of 1000 mg/kg bw/day. Based on these results, the doses in the main study were determined to be 100, 300 and 1000 mg/kg bw/day. - Rationale for animal assignment: Body weight-balanced randomization |

**Examinations**

***Observations and examinations performed and frequency***

|  |
| --- |
| CAGE SIDE OBSERVATIONS: Yes  - Time schedule: Daily BODY WEIGHT: Yes - Time schedule for examinations:  Male: Body weights were determined on days 1 (before dosing), 8, 15, 22, 29, 36, 42 and 43 (at autopsy) in males. Female: Body weights were determined on days 1 (before dosing), 8 and 15 in all females, on day 22 in some females, on days 0, 7, 14 and 20 of gestation in pregnant females, on days 0 and 4 (at autopsy) of lactation in females that delivered.  FOOD CONSUMPTION: Yes - Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes - Time schedule for examinations:  Male: Food consumption was determined for the same days as measurement of body weight except the mating period in males.  Female: Food consumption was determined for the same days as measurement of body weight except the mating period in all females, for days 0-7, 7-14 and 14-20 of gestation in pregnant females, and for days 0-4 of lactation in females that delivered.  FOOD EFFICIENCY: No WATER CONSUMPTION: No OPHTHALMOSCOPIC EXAMINATION: No HAEMATOLOGY: Yes (male only) - Time schedule for collection of blood: On the day following the end of the administration period.  - Anaesthetic used for blood collection: Yes. Anesthetized with sodium pentobarbital. - Animals fasted: Yes. 18 - 24 hrs after the administration period - How many animals: All males: 52 males (13 males/dose) - Parameters examined: Red blood cell (RBC), White blood cell (WBC), Hemoglobin (Hb), Mean erythrocyte corpuscular volume (MCV), Platelet, Hematocrit (Ht), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Differentiation of leukocyte CLINICAL CHEMISTRY: Yes (male only) - Time schedule for collection of blood: On the day following the end of the administration period. - Animals fasted: Yes. 18 - 24 hrs after the administration period - How many animals: All males: 52 males (13 males/dose) - Parameters examined: T. protein, albumin, A/G, BUN, creatinine, glucose, T. cholesterol, T. bilirubin, triglyceride, sodium, potassium, chloride, calcium, I. phosphorus, ALP, GPT, GOT and gamma-GTP. URINALYSIS: No  NEUROBEHAVIOURAL EXAMINATION: No |

***Sacrifice and pathology***

|  |
| --- |
| GROSS PATHOLOGY: Yes   HISTOPATHOLOGY: Yes Brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder and uterus were preserved in 10% buffered formalin solution, and testes, epididymides and ovaries were preserved in Bouin’s fluid. - Histopathological examined organ: Male: Control and 1000 mg/kg bw/day groups: Brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder, testes and epididymides Female: Control and 1000 mg/kg bw/day groups: Brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder and uterus. Non-pregnant females: ovaries  ORGAN WEIGHTS: Yes - Weighted organ: Male: All groups of males: Thymus, liver, kidneys, testes and epididymides. Female: All groups of females: Thymus, liver and kidneys. |

***Statistics***

|  |
| --- |
| Statistical analyses were conducted using Bartlett’s test, one way ANOVA, Dunnett’s or Scheffe’s pair wise comparison test, Kruskal-Wallis rank sum test and Mann-Whitney U- test. |

**Results and discussions**

**Effect levels**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endpoint** | **Effect level** | **Based on** | **Sex** | **Basis for effect level / Remarks** |
| NOAEL | 300 mg/kg bw/day (actual dose received) |  | male/female | Increases in GOT and GPT, and a decrease in glucose were found in males in the 1000 mg/kg bw/day group, and decreases in body weight and body weight gain were observed in pregnant females in the 1000 mg/kg bw/day group at gestation period. |

**Results of examinations**

***Clinical signs and mortality***

|  |
| --- |
| no effects |

***Body weight and weight gain***

|  |
| --- |
| yes |

***Food consumption and compound intake (if feeding study)***

|  |
| --- |
| no effects |

***Food efficiency***

|  |
| --- |
| not examined |

***Water consumption and compound intake (if drinking water study)***

|  |
| --- |
| not examined |

***Ophthalmoscopic examination***

|  |
| --- |
| not examined |

***Haematology***

|  |
| --- |
| no effects |

***Clinical chemistry***

|  |
| --- |
| yes |

***Urinalysis***

|  |
| --- |
| not examined |

***Neurobehaviour***

|  |
| --- |
| not examined |

***Organ weights***

|  |
| --- |
| no effects |

***Gross pathology***

|  |
| --- |
| no effects |

***Histopathology: non-neoplastic***

|  |
| --- |
| no effects |

***Histopathology: neoplastic***

|  |
| --- |
| no data |

***Details on results***

|  |
| --- |
| CLINICAL SIGNS AND MORTALITY Mortality: No animal died in any group. Clinical signs: There were no treatment-related clinical signs in any group.  BODY WEIGHT AND WEIGHT GAIN (Table 1) Male: There were no changes related to the test substance in any group. Female: Body weight at gestation day 20 and body weight gain during the pregnancy period was slightly but significantly suppressed in the 1000 mg/kg bw/day group.  FOOD CONSUMPTION There were no changes related to the test substance in any group.  HAEMATOLOGY (Table 2): male Statistically significant changes were observed in hematocrit, MCHC, segmented neutrophil, lymphocyte, but these changes are considered unrelated to the test substance.  CLINICAL CHEMISTRY(Table 3): male Statistically significant changes were observed in A/G ratio, creatinine, glucose, Na, K, Cl, GOT, GPT and γ-GTP. Significant increases in GOT and GPT, and a significant decrease in glucose observed in males in the 1000 mg/kg bw/day group may indicate adverse effects on the liver. Other slight or dose independent changes are considered non-toxicological effects.  ORGAN WEIGHTS (Table 4) There were no changes related to the test substance in any group (a decrease in absolute/relative liver weight at 100 mg/kg bw/day was dose independent).  GROSS PATHOLOGY There were no changes related to the test substance in any group.  HISTOPATHOLOGY: NON-NEOPLASTIC (Table 5) There were no changes related to the test substance in any group. |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1. Body weight of female rats   |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) | 0 |  | 100 |  | 300 |  | 1000 |  | | Day of administration |  |  |  |  |  |  |  |  | | (Pre-mating days) |  |  |  |  |  |  |  |  | | 1 | 210.3 ± 6.9 | (13) | 210.8 ± 6.7 | (13) | 210.9 ± 6.3 | (13) | 211.1 ± 7.0 | (13) | | 8 | 226.9 ± 7.0 | (13) | 225.4 ± 9.6 | (13) | 231.4 ± 9.2 | (13) | 228.4 ± 10.6 | (13) | | 15 | 236.8 ± 7.7 | (13) | 234.8 ± 12.2 | (13) | 247.3 ± 12.7 | (13) | 242.3 ± 13.6 | (13) | | Days of pregnancy |  |  |  |  |  |  |  |  | | 0 | 245.2 ± 10.0 | (12) | 245.1 ± 13.5 | (12) | 256.6 ± 13.2 | (10) | 244.6 ± 13.1 | (12) | | 7 | 282.5 ± 12.9 | (12) | 283.3 ± 17.9 | (12) | 296.6 ± 21.0 | (10) | 278.4 ± 14.0 | (12) | | 14 | 323.2 ± 20.3 | (12) | 319.2 ± 24.0 | (12) | 336.3 ± 23.7 | (10) | 311.5 ± 15.0 | (12) | | 20 | 400.1 ± 24.9 | (12) | 390.5 ± 29.6 | (12) | 403.4 ± 20.4 | (10) | 375.8 ± 17.9\* | (12) | | Days of lactation |  |  |  |  |  |  |  |  | | 0 | 282.1 ± 17.1 | (12) | 287.7 ± 23.6 | (12) | 309.3 ± 32.3 | (10) | 281.8 ± 29.0 | (12) | | 4 | 299.5 ± 14.0 | (12) | 300.9 ± 17.8 | (12) | 324.2 ± 25.8\* | (10) | 303.4 ± 24.9 | (12) |   Values are expressed as mean ± S.D.  \*: significant difference from control, p <0.05  Table 2. Hematological findings of male rats   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) | 0 | 100 | 300 | 1000 | | No. of animals | 13 | 13 | 13 | 13 | | Red blood cells |  |  |  |  | | Count (X104/mm3) | 808 ± 39 | 794 ± 36 | 806 ± 36 | 82.5 ± 34 | | Hemoglobin (g/dl) | 15.5 ± 0.4 | 15.2 ± 0.8 | 15.4 ± 0.4 | 15.8 ± 0.4 | | Hematocrit (%) | 45.5 ± 1.1 | 44.6 ± 1.9 | 45.8 ± 1.3 | 47.0 ± 1.6\* | | MCV (μm3) | 56.4 ± 1.7 | 56.2 ± 1.6 | 56.9 ± 2.2 | 56.9 ± 1.6 | | MCH (pg) | 19.3 ± 0.7 | 19.1 ± 0.7 | 19.1 ± 0.8 | 19.2 ± 0.7 | | MCHC (%) | 34.2 ± 0.4 | 34.0 ± 0.4 | 33.6 ± 0.3\*\* | 33.7 ± 0.6\* | | White blood cells |  |  |  |  | | Count (X102/mm3) | 88 ± 25 | 73 ± 18 | 72 ± 23 | 92 ± 21 | | Band neutrophil (%) | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | | Segmented neutrophil (%) | 17 ± 12 | 18 ± 6 | 30 ± 15\*\* | 23 ± 7 | | Eosinophil (%) | 1 ± 1 | 0 ± 1 | 1 ± 2 | 1 ± 1 | | Basophil (%) | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | | Monocyte (%) | 2 ± 2 | 3 ± 2 | 5 ± 3 | 4 ± 3 | | Lymphocyte (%) | 79 ± 13 | 78 ± 6 | 64 ± 13\*\* | 72 ± 8\* | | Platelet |  |  |  |  | | Count (X104/mm3) | 100.1 ± 7.0 | 101.1 ± 8.6 | 101.9 ± 10.9 | 104.9 ± 8.6 |   Values are expressed as mean ± S.D.  \*: significant difference from control, p< 0.05  \*\*: significant difference from control, p<0.01  Table 3. Blood chemical findings of male rats   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) | 0 | 100 | 300 | 1000 | | No. of animals | 13 | 13 | 13 | 13 | | Total protein (g/dl) | 5.4 ± 0.3 | 5.3 ± 0.2 | 5.4 ± 0.3 | 5.7 ± 0.2\* | | Albumin (g/dl) | 2.9 ± 0.2 | 2.9 ± 0.2 | 2.9 ± 0.2 | 3.0 ± 0.2 | | A/G ratio | 1.11 ± 0.09 | 1.22 ± 0.09\* | 1.13 ± 0.10 | 1.10 ± 0.11 | | BUN (mg/dl) | 19 ± 4 | 17 ± 2 | 19 ± 2 | 20 ± 2 | | Creatinine (mg/dl) | 0.8 ± 0.1 | 0.7 ± 0.1\* | 0.7 ± 0.1 | 0.7 ± 0.1\* | | Glucose (mg/dl) | 149 ± 18 | 133 ± 12 | 132 ± 8 | 113 ± 9\*\* | | Total cholesterol (mg/dl) | 50 ± 10 | 43 ± 9 | 45 ± 9 | 50 ± 9 | | Total bilirubin (mg/dl) | 0.08 ± 0.03 | 0.09 ± 0.03 | 0.09 ± 0.02 | 0.09 ± 0.02 | | Triglyceride (mg/dl) | 67 ± 28 | 49 ± 16 | 50 ± 15 | 46 ± 13 | | Na (mEq/l) | 143.1 ± 0.4 | 143.7 ± 0.7 | 143.4 ± 1.0 | 144.6 ± 1.0\*\* | | K (mEq/l) | 3.93 ± 0.18 | 4.13 ± 0.30 | 3.93 ± 0.29 | 3.61 ± 0.19\*\* | | Cl (mEq/l) | 105.9 ± 1.0 | 107.4 ± 1.2\*\* | 107.3 ± 1.0\* | 107.6 ± 1.6\*\* | | Ca (mg/dl) | 8.5 ± 0.3 | 8.4 ± 0.2 | 8.4 ± 0.3 | 8.5 ± 0.2 | | Inorg. Phos. (mg/dl) | 5.5 ± 0.5 | 5.6 ± 0.5 | 5.4 ± 0.5 | 5.5 ± 0.3 | | ALP (IU/l) | 206 ± 53 | 234 ± 41 | 195 ± 29 | 203 ± 38 | | GPT (IU/l) | 27 ± 4 | 26 ± 5 | 29 ± 8 | 34 ± 6\* | | GOT (IU/l) | 61 ± 11 | 61 ± 6 | 73 ± 17 | 82 ± 20\*\* | | γ-GTP (IU/l) | 0 ± 0 | 0 ± 0 | 0 ± 1\* | 0 ± 1\* |   Values are expressed as mean ± S.D.  \*: significant difference from control, p<0.05  \*\*: significant difference from control, p<0.01  Table 4. Absolute and relative organ weights of rats   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) |  | 0 | 100 | 300 | 1000 | | Male |  |  |  |  |  | | Number of animals |  | 13 | 13 | 13 | 13 | | Final body weight |  | 474.9 ± 39.4 | 454.8 ± 26.9 | 473.6 ± 49.5 | 459.1 ± 36.4 | | Liver | Absolute (g) | 13.56 ± 2.03 | 11.63 ± 1.02\* | 12.82 ± 1.95 | 12.55 ± 1.39 | |  | Relative (g/100g) | 2.84 ± 0.23 | 2.56 ± 0.17\*\* | 2.70 ± 0.17 | 2.73 ± 0.13 | | Kidney | Absolute (g) | 2.93 ± 0.24 | 2.82 ± 0.19 | 2.99 ± 0.27 | 2.84 ± 0.27 | |  | Relative (g/100g) | 0.62 ± 0.04 | 0.62 ± 0.04 | 0.63 ± 0.06 | 0.62 ± 0.04 | | Thymus | Absolute (mg) | 354.0 ± 78.8 | 314.6 ± 62.3 | 344.5 ± 61.0 | 342.0 ± 100.7 | |  | Relative (mg/100g) | 75.3 ± 18.9 | 69.0 ± 11.7 | 73.1 ± 12.1 | 73.7 ± 17.7 | | Testis | Absolute (g) | 3.17 ± 0.23 | 3.13 ± 0.21 | 3.20 ± 0.25 | 3.08 ± 0.18 | |  | Relative (g/100g) | 0.67 ± 0.07 | 0.69 ± 0.07 | 0.68 ± 0.08 | 0.67 ± 0.06 | | Epididymides | Absolute (g) | 1.14 ± 0.13 | 1.13 ± 0.10 | 1.13 ± 0.11 | 1.13 ± 0.08 | |  | Relative (g/100g) | 0.24 ± 0.03 | 0.25 ± 0.03 | 0.24 ± 0.02 | 0.25 ± 0.02 | |  |  |  |  |  |  | | Female |  |  |  |  |  | | Number of animals |  | 12 | 12 | 10 | 12 | | Final body weight |  | 299.5 ± 14.0 | 300.9 ± 17.8 | 324.3 ± 25.8\* | 303.4 ± 24.9 | | Liver | Absolute (g) | 12.92 ± 1.29 | 12.28 ± 1.25 | 13.40 ± 1.37 | 12.60 ± 1.55 | |  | Relative (g/100g) | 4.31 ± 0.38 | 4.08 ± 0.33 | 4.14 ± 0.32 | 4.16 ± 0.42 | | Kidney | Absolute (g) | 1.97 ± 0.24 | 1.87 ± 0.21 | 2.06 ± 0.22 | 1.89 ± 0.13 | |  | Relative (g/100g) | 0.66 ± 0.08 | 0.62 ± 0.07 | 0.63 ± 0.04 | 0.63 ± 0.06 | | Thymus | Absolute (mg) | 150.0 ± 61.7 | 165.1 ± 47.7 | 213.2 ± 62.5 | 184.3 ± 62.5 | |  | Relative (mg/100g) | 50.4 ± 21.7 | 54.6 ± 14.6 | 65.1 ± 15.6 | 60.1 ± 18.2 |   Values are expressed as mean ± S.D.  \*: significant difference from control, p<0.05  \*\*: significant difference from control, p<0.01  Table 5. Histopathological findings of rats   |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | |  | Sex | Male | | | |  | Female | | | | | Organ findings | Dose  (mg/kg bw/day) | 0 | 100 | 300 | 1000 |  | 0 | 100 | 300 | 1000 | |  | <Grade> |  |  |  |  |  |  |  |  |  | | Brain |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Congenital defect, cerebral cortex, unilateral | total | 1 |  |  | 0 |  | 0 |  |  | 0 | |  | + | 1 |  |  | 0 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Liver |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Degeneration, fatty, hepatocyte, periportal | total | 13 |  |  | 13 |  | 9 |  |  | 10 | |  | ± | 2 |  |  | 4 |  | 7 |  |  | 8 | |  | + | 11 |  |  | 9 |  | 2 |  |  | 2 | | Microgranuloma | total | 13 |  |  | 12 |  | 10 |  |  | 12 | |  | ± | 11 |  |  | 11 |  | 10 |  |  | 12 | |  | + | 2 |  |  | 1 |  | 0 |  |  | 0 | | Necrosis, focal | total | 1 |  |  | 1 |  | 0 |  |  | 0 | |  | + | 1 |  |  | 1 |  |  |  |  |  | | Hemorrhage, focal | total | 1 |  |  | 1 |  | 0 |  |  | 0 | |  | ± | 1 |  |  | 0 |  |  |  |  |  | |  | + | 0 |  |  | 1 |  |  |  |  |  | | Fibrosis, capsule, focal | total | 0 |  |  | 1 |  | 0 |  |  | 0 | |  | ± | 0 |  |  | 1 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Kidney |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Eosinophilic body | total | 7 |  |  | 6 |  | 0 |  |  | 0 | |  | ± | 3 |  |  | 4 |  |  |  |  |  | |  | + | 3 |  |  | 2 |  |  |  |  |  | |  | ++ | 1 |  |  | 0 |  |  |  |  |  | | Basophilic tuble | total | 7 |  |  | 4 |  | 4 |  |  | 6 | |  | ± | 6 |  |  | 4 |  | 4 |  |  | 6 | |  | + | 1 |  |  | 0 |  | 0 |  |  | 0 | | Cast, hyaline, cortico-medullary junction | total | 1 |  |  | 0 |  | 0 |  |  | 0 | |  | ± | 0 |  |  | 0 |  |  |  |  |  | |  | + | 1 |  |  | 0 |  |  |  |  |  | | Dilatation, pelvis | total | 1 |  |  | 0 |  | 0 |  |  | 0 | |  | + | 1 |  |  | 0 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Spleen |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Hematopoiesis, extramedullary | total | 13 |  |  | 13 |  | 13 |  |  | 13 | |  | ± | 12 |  |  | 12 |  | 3 |  |  | 5 | |  | + | 1 |  |  | 1 |  | 8 |  |  | 6 | |  | ++ | 0 |  |  | 0 |  | 2 |  |  | 2 | | Deposit, pigment, brown | total | 13 |  |  | 13 |  | 13 |  |  | 13 | |  | ± | 5 |  |  | 7 |  | 1 |  |  | 3 | |  | + | 8 |  |  | 6 |  | 7 |  |  | 9 | |  | ++ | 0 |  |  | 0 |  | 5 |  |  | 1 | |  |  |  |  |  |  |  |  |  |  |  | | Thymus |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Atrophy | total | 0 |  |  | 0 |  | 7 |  |  | 4 | |  | ± |  |  |  |  |  | 5 |  |  | 4 | |  | + |  |  |  |  |  | 1 |  |  | 0 | |  | ++ |  |  |  |  |  | 1 |  |  | 0 | |  |  |  |  |  |  |  |  |  |  |  | | Heart |  | [13] | [0] | [0] | [13] |  | [13] | [0] | [0] | [13] | | Myocardial degeneration, focal | total | 1 |  |  | 0 |  | 0 |  |  | 0 | |  | ± | 1 |  |  | 0 |  |  |  |  |  | | Myocardial fibrosis, focal | total | 0 |  |  | 1 |  | 0 |  |  | 0 | |  | ± | 0 |  |  | 1 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Testis |  | [13] | [0] | [0] | [13] |  | [0] | [0] | [0] | [0] | | Atrophy, seminiferous, tubule, focal | total | 0 |  |  | 1 |  |  |  |  |  | |  | ± | 0 |  |  | 1 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Epididymis |  | [13] | [0] | [0] | [13] |  | [0] | [0] | [0] | [0] | | Cell debris, tubular lumen | total | 0 |  |  | 1 |  |  |  |  |  | |  | ± | 0 |  |  | 1 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  | | Ovary |  | [0] | [0] | [0] | [0] |  | [1] | [1] | [3] | [1] | | Abnormality | total |  |  |  |  |  | 0 | 0 | 0 | 0 |   ±: Very slight; +: Slight; ++: Moderate  [ ]: Number of animals examined |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| In a combined repeated dose toxicity/reproductive toxicity study (OECD TG 422), rats were treated orally for 42-54 days. No treatment-related effects were observed in clinical signs, food consumption, hematology (examined only in males), organ weight and the histopathological appearance of tissues from the major organs including the liver. In clinical chemistry (examined only in males), significant but slight increases in GOT and GPT, reflecting an effect on liver function, and a slight decrease in glucose were observed at 1,000 mg/kg bw/day. Based on no histopathological changes in the liver, these changes in clinical chemistry were not considered to be toxicologically important. A significant but slight decrease in body weight gain was observed in pregnant females at 1,000 mg/kg bw/day. However this change was observed only in the late period of pregnancy. Based on the above findings, the NOAEL was considered to be 1000 mg/kg bw/day in both sexes. |

**7.6 Genetic toxicity**

**7.6.1 Genetic toxicity in vitro**

***Endpoint study record: Genetic toxicity in vitro.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-45948654-faf3-4104-b204-71b36c8ed66e |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:05 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | Reverse Mutation Test of 1,1,1-Tris(hydroxymethyl)ethane on Bacteria. | Toxicity Testing Reports of Environmental Chemicals, 6, 54-57 | Biosafety Research Center, Foods, Drugs and Pesticides (Anpyo Center) |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Type of genotoxicity**

|  |
| --- |
| gene mutation |

**Type of study**

|  |
| --- |
| bacterial reverse mutation assay (e.g. Ames test) |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 471 (Bacterial Reverse Mutation Assay) | no |
| according to | OECD Guideline 472 (Genetic Toxicology: Escherichia coli, Reverse Mutation Assay) | no |
| according to | JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals | no |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: Solid matter - Analytical purity: 99.0% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Method**

**Species/strain**

|  |  |
| --- | --- |
| **Species/strain** | other: Salmonella typhimurium TA1535, TA1537, TA98, TA100 and Escherichia coli WP2 uvrA |
| **Metabolic activation** | with and without |
| **Metabolic activation system** | rat liver, induced by phenobarbital and 5,6-benzoflavone |

**Test concentrations**

|  |
| --- |
| -S9 mix: 156, 313, 625, 1250, 2500, 5000 μg/plate (all strains) +S9 mix: 156, 313, 625, 1250, 2500, 5000 μg/plate (all strains) |

***Vehicle***

|  |
| --- |
| - Vehicle(s)/solvent(s) used: Distilled water |

**Controls**

|  |  |
| --- | --- |
| **Negative controls** | no |
| **Solvent / vehicle controls** | yes |
| **True negative controls** | no |
| **Positive controls** | yes |
| **Positive control substance** | other: -S9 mix: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (TA 100, TA98 and WP2 uvrA), sodium azide (TA1535) and 9-aminoacridine hydrochloride (TA1537). +S9 mix: 2-aminoanthracene (all strains) |

***Details on test system and conditions***

|  |
| --- |
| METHOD OF APPLICATION: Preincubation  DURATION - Preincubation period: 20 min at 37 ℃ - Exposure duration:48 hrs  NUMBER OF PLATES: 3  NUMBER OF REPLICATIONS: 2   DETERMINATION OF CYTOTOXICITY - Method: other: growth inhibition |

***Evaluation criteria***

|  |
| --- |
| In any strain(s) tested with or without S9 mix, when the mean number of revertant colonies per plate increased twice more than that of the negative control and when the increase was shown to be dose-related and reproducible, the chemical was judged mutagenic. |

***Statistics***

|  |
| --- |
| No |

**Results and discussions**

**Test results**

|  |  |
| --- | --- |
| **Species/strain** | other: Salmonella typhimurium TA1535, TA1537, TA98, TA100 and Escherichia coli WP2 uvrA |
| **Metabolic activation** | with and without |
| **Test system** | all strains/cell types tested |
| **Genotoxicity** | negative |
| **Cytotoxicity** | no |
| **Vehicle controls valid** | yes |
| **Negative controls valid** | not examined |
| **Positive controls valid** | yes |

***Additional information on results***

|  |
| --- |
| RANGE-FINDING/SCREENING STUDIES: Concentration: 19.5, 78.1, 313 and 1250 μg/plate Cytotoxic conc.: No |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| [1st trial] See Table 1 and Table 2  -S9 mix: Negative (all test strains)  +S9 mix: Negative (all test strains)  [2nd trial] See Table 3 and Table 4  -S9 mix: Negative (all test strains)  +S9 mix: Negative (all test strains)  Table 1. Results of the bacterial reversion test of 1,1,1 -tris(hydroxymethyl)ethane (1st trial) (direct method: -S9 mix)   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/plate) | Revertants colonies per plate [Mean ± SD ] | | | | | | TA100 | TA1535 | WP2uvrA | TA98 | TA1537 | | Test substance | 0 | 102, 116, 108  [ 109 ± 7 ] | 10, 10, 10  [ 10 ± 0 ] | 21, 22, 21  [ 21 ± 1 ] | 27, 23, 28  [ 26 ± 3 ] | 8, 8, 7  [ 8 ± 1 ] | | 156 | 126, 111, 110  [ 116 ± 9 ] | 17, 10, 10  [ 12 ± 4 ] | 21, 22, 25  [ 23 ± 2 ] | 27, 25, 23  [ 25 ± 2 ] | 9, 6, 8  [ 8 ± 2 ] | | 313 | 104, 103, 107  [ 105 ± 2 ] | 11, 10, 9  [ 10 ± 1 ] | 23, 19, 24  [ 22 ± 3 ] | 20, 25, 23  [ 23 ± 3 ] | 11, 14, 9  [ 11 ± 3 ] | | 625 | 106, 105, 100  [ 104 ± 3 ] | 7, 11, 10  [ 9 ± 2 ] | 22, 20, 23  [ 22 ± 2 ] | 21, 22, 23  [ 22 ± 1 ] | 6, 9, 5  [ 7 ± 2 ] | | 1250 | 96, 109, 110  [ 105 ± 8 ] | 10, 8, 15  [ 11 ± 4 ] | 22, 24, 23  [ 23 ± 1 ] | 20, 25, 19  [ 21 ± 3 ] | 13, 7, 10  [ 10 ± 3 ] | | 2500 | 102, 101, 100  [ 101 ± 1 ] | 8, 9, 5  [ 7 ± 2 ] | 18, 24, 15  [ 19 ± 5 ] | 24, 19, 18  [ 20 ± 3 ] | 6, 10, 6  [ 7 ± 2 ] | | 5000 | 93, 98, 98  [ 96 ± 3 ] | 5, 9, 5  [ 6 ± 2 ] | 17, 20, 24  [ 20 ± 4) | 16, 15, 17  [ 16 ± 1) | 9, 9, 4  [ 7 ± 3 ] | | Positive control | Chemical | AF2 | NaN3 | AF2 | AF2 | 9AA | | Dose(μg/plate) | 0.01 | 0.5 | 0.01 | 0.1 | 80 | | Number of  colonies/plate | 767, 786, 763  [ 772 ± 13 ] | 405, 402, 380  [ 396 ± 14 ] | 183, 186, 167  [ 179 ± 10 ] | 455, 456, 483  [ 465 ± 16 ] | 457, 440, 431  [ 443 ± 13 ] |   AF-2; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide NaN3 ; Sodium azide 9-AA ; 9-Aminoacridine hydrochloride  Table 2. Results of the bacterial reversion test of 1,1,1 -tris(hydroxymethyl)ethane (1st trial) (activation method: +S9 mix)   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/plate) | Revertants colonies per plate [Mean ± SD ] | | | | | | TA100 | TA1535 | WP2uvrA | TA98 | TA1537 | | Test substance | 0 | 100, 108, 116  [ 108 ± 8 ] | 13, 13, 10  [ 12 ± 2) | 21, 26, 24  [ 24 ± 3 ] | 22, 26, 30  [ 26 ± 4 ] | 10, 10, 11  [ 10 ± 1 ] | | 156 | 120, 103, 105  [ 109 ± 9 ] | 15, 11, 10  [ 12 ± 3 ] | 22, 26, 27  [ 25 ± 3 ] | 31, 25, 27  [ 28 ± 3 ] | 8, 9, 11  [ 9 ± 2 ] | | 313 | 114, 106, 111  [ 110 ± 4 ] | 13, 17, 16  [ 15 ± 2 ] | 24, 22, 25  [ 24 ± 2 ] | 33, 34, 30  [ 32 ± 2 ] | 9, 11, 14  [ 11 ± 3 ] | | 625 | 114, 99, 112  [ 108 ± 8 ] | 11, 11, 16  [ 13 ± 3 ] | 23, 26, 26  [ 25 ± 2 ] | 24, 29, 24  [ 26 ± 3 ] | 16, 11, 14  [ 14 ± 3 ] | | 1250 | 98, 104, 102  [ 101 ± 3 ] | 13, 17, 10  [ 13 ± 4 ] | 22, 27, 22  [ 24 ± 3 ] | 28, 29, 28  [ 28 ± 1 ] | 13, 9, 11  [ 11 ± 2 ] | | 2500 | 103, 94, 101  [ 99 ± 5 ] | 10, 12, 8  [ 10 ± 2 ] | 20, 29, 23  [ 24 ± 5 ] | 29, 24, 22  [ 25 ± 4 ] | 8, 11, 11  [ 10 ± 2 ] | | 5000 | 96, 91, 87  [ 91 ± 5 ] | 8, 8, 9  [ 8 ± 1 ] | 19, 23, 18  [ 20 ± 3) | 25, 29, 20  [ 25 ± 5) | 14, 9, 14  [ 12 ± 3 ] | | Positive control | Chemical | 2AA | 2AA | 2AA | 2AA | 2AA | | Dose(μg/plate) | 1 | 2 | 10 | 0.5 | 2 | | Number of  colonies/plate | 405, 407, 420  [ 411 ± 8 ] | 283, 329, 306  [ 306 ± 23 ] | 513, 525, 499  [ 512 ± 13 ] | 240, 224, 266  [ 243 ± 21 ] | 143, 188, 164  [ 165 ± 23 ] |   2-AA ; 2-Aminoanthracene  Table 3. Results of the bacterial reversion test of 1,1,1 -tris(hydroxymethyl)ethane (2nd trial) (direct method: -S9 mix)   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/plate) | Revertants colonies per plate [Mean ± SD ] | | | | | | TA100 | TA1535 | WP2uvrA | TA98 | TA1537 | | Test substance | 0 | 99, 110, 109  [ 106 ± 6 ] | 15, 15, 14  [ 15 ± 1 ] | 22, 25, 20  [ 22 ± 3 ] | 24, 22, 25  [ 24 ± 2 ] | 9, 8, 11  [ 9 ± 2 ] | | 156 | 111, 115, 100  [ 109 ± 8 ] | 15, 10, 13  [ 13 ± 3 ] | 24, 24, 25  [ 24 ± 1 ] | 24, 27, 21  [ 24 ± 3 ] | 8, 14, 13  [ 12 ± 3 ] | | 313 | 92, 107, 105  [ 101 ± 8 ] | 18, 10, 12  [ 13 ± 4 ] | 24, 20, 19  [ 21 ± 3 ] | 26, 23, 24  [ 24 ± 2 ] | 9, 14, 11  [ 11 ± 3 ] | | 625 | 101, 109, 104  [ 105 ± 4 ] | 14, 18, 14  [ 15 ± 2 ] | 21, 23, 23  [ 22 ± 1 ] | 23, 21, 22  [ 22 ± 1 ] | 16, 13, 13  [ 14 ± 2 ] | | 1250 | 107, 101, 117  [ 108 ± 8 ] | 11, 10, 11  [ 11 ± 1 ] | 23, 18, 23  [ 21 ± 3 ] | 24, 27, 22  [ 24 ± 3 ] | 11, 10, 5  [ 9 ± 3 ] | | 2500 | 98, 100, 102  [ 100 ± 2 ] | 10, 16, 13  [ 13 ± 3 ] | 29, 23, 20  [ 24 ± 5 ] | 20, 22, 23  [ 22 ± 2 ] | 10, 14, 9  [ 11 ± 3 ] | | 5000 | 96, 88, 91  [ 92 ± 4 ] | 17, 14, 15  [ 15 ± 2 ] | 22, 22, 17  [ 20 ± 3 ] | 24, 26, 22  [ 24 ± 2 ] | 10, 15, 10  [ 12 ± 3 ] | | Positive control | Chemical | AF2 | NaN3 | AF2 | AF2 | 9AA | | Dose(μg/plate) | 0.01 | 0.5 | 0.01 | 0.1 | 80 | | Number of  colonies/plate | 729, 702, 722  [ 718 ± 14 ] | 310, 318, 330  [ 319 ± 10 ] | 164, 195, 188  [ 182 ± 16 ] | 432, 406, 402  [ 413 ± 16 ] | 441, 421, 410  [ 424 ± 16 ] |   AF-2; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide NaN3 ; Sodium azide 9-AA ; 9-Aminoacridine hydrochloride  Table 4. Results of the bacterial reversion test of 1,1,1 -tris(hydroxymethyl)ethane (2nd trial) (activation method: +S9 mix)   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/plate) | Revertants colonies per plate [Mean ± SD ] | | | | | | TA100 | TA1535 | WP2uvrA | TA98 | TA1537 | | Test substance | 0 | 119, 103, 116  [ 113 ± 9 ] | 14, 14, 10  [ 13 ± 2) | 26, 20, 23  [ 23 ± 3 ] | 33, 27, 30  [ 30 ± 3 ] | 9, 10, 13  [ 11 ± 2 ] | | 156 | 109, 103, 116  [ 109 ± 7 ] | 14, 17, 16  [ 16 ± 2 ] | 26, 22, 24  [ 24 ± 2 ] | 28, 23, 23  [ 25 ± 3 ] | 10, 11, 9  [ 10 ± 1 ] | | 313 | 128, 125, 102  [ 118 ± 14 ] | 16, 10, 13  [ 13 ± 3 ] | 21, 23, 28  [ 24 ± 4 ] | 27, 31, 26  [ 28 ± 3 ] | 10, 13, 13  [ 12 ± 2 ] | | 625 | 117, 127, 120  [ 121 ± 5 ] | 13, 13, 13  [ 13 ± 0 ] | 25, 22, 21  [ 23 ± 2 ] | 24, 27, 32  [ 28 ± 4 ] | 16, 11, 11  [ 13 ± 3 ] | | 1250 | 105, 122, 122  [ 116 ± 10 ] | 18, 13, 18  [ 16 ± 3 ] | 23, 22, 25  [ 23 ± 2 ] | 28, 34, 29  [ 30 ± 3 ] | 10, 11, 13  [ 11 ± 2 ] | | 2500 | 132, 113, 109  [ 118 ± 12 ] | 10, 13, 16  [ 13 ± 3 ] | 25, 24, 20  [ 23 ± 3 ] | 25, 26, 34  [ 28 ± 5 ] | 11, 15, 17  [ 14 ± 3 ] | | 5000 | 105, 100, 106  [ 104 ± 3 ] | 10, 10, 6  [ 9 ± 2 ] | 24, 20, 26  [ 23 ± 3 ] | 22, 28, 30  [ 27 ± 4 ] | 11, 13, 8  [ 11 ± 3 ] | | Positive control | Chemical | 2AA | 2AA | 2AA | 2AA | 2AA | | Dose(μg/plate) | 1 | 2 | 10 | 0.5 | 2 | | Number of  colonies/plate | 366, 380, 380  [ 375 ± 8 ] | 310, 310, 313  [ 311 ± 2 ] | 460, 447, 451  [ 453 ± 7 ] | 255, 295, 250  [ 267 ± 25 ] | 187, 169, 170  [ 175 ± 10 ] |   2-AA ; 2-Aminoanthracene |

**Overall remarks, attachments**

**Overall remarks**

|  |
| --- |
| No increase in revertant colonies was observed in the test with either the non-activation method (-S9) or activation (+S9) method. Reverse mutation assays using microorganisms (Salmonella typhimurium, Escherichia coli) were conducted to assess the potential of 1,1,1 -tris(hydroxymethyl)ethane to induce gene mutations. 1,1,1-Tris(hydroxymethyl)ethane did not induce gene mutations in the bacteria under the conditions of this study. The positive control showed expected results. |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| 1,1,1-Tris(hydroxymethyl)ethane did not induce gene mutations in the in vitro bacteria test. |

***Endpoint study record: Genetic toxicity in vitro.002***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-209802c0-6880-43ba-a6e2-e91ecc3bcc3a |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:05 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | In Vitro Chromosomal Aberration Test of 1,1,1-Tris(hydroxymethyl)ethane on Cultured Chinese Hamster Cells. | Toxicity Testing Reports of Environmental Chemicals, 6, 58-61 | Biosafety Research Center, Foods, Drugs and Pesticides (Anpyo Center) |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Materials and methods**

**Type of genotoxicity**

|  |
| --- |
| chromosome aberration |

**Type of study**

|  |
| --- |
| in vitro mammalian chromosome aberration test |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) | no |
| according to | JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals | no |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: Solid matter - Analytical purity: 99.0% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Method**

**Target gene**

|  |
| --- |
| Chromosome |

**Species/strain**

|  |  |
| --- | --- |
| **Species/strain** | other: Chinese hamster lung(CHL/IU) cells |
| **Metabolic activation** | with and without |
| **Metabolic activation system** | rat liver, induced by phenobarbital and 5,6-benzoflavone |

**Test concentrations**

|  |
| --- |
| -S9 mix (continuous treatment): 0, 300, 600, 1200 ug/mL -S9 mix (short-term treatment): 0, 300, 600, 1200 ug/mL +S9 mix (short-term treatment): 0, 300, 600, 1200 ug/mL |

***Vehicle***

|  |
| --- |
| - Vehicle(s)/solvent(s) used: Saline |

**Controls**

|  |  |
| --- | --- |
| **Negative controls** | no |
| **Solvent / vehicle controls** | yes |
| **True negative controls** | no |
| **Positive controls** | yes |
| **Positive control substance** | other: [continuous treatment]: mitomycin C; [short-term treatment, -S9 & +S9]: cyclophsophamide |

***Details on test system and conditions***

|  |
| --- |
| METHOD OF APPLICATION:  Exposure duration:  [continuous treatment]:  24 hrs or 48 hrs [short-term treatment]: 6 hrs + 18 hr recovery period  - Fixation time (start of exposure up to fixation or harvest of cells): Continuous treatment: 24 hrs or 48 hrs Short-term treatment: 24 hrs  SPINDLE INHIBITOR: Colcemid  STAIN: Giemsa stain  NUMBER OF REPLICATIONS: 2 NUMBER OF CELLS EVALUATED: 200 cells / dose DETERMINATION OF CYTOTOXICITY -Method: relative total growth |

***Evaluation criteria***

|  |
| --- |
| For the evaluation of the frequencies of structural aberrations and of polyploidy induced, the following criteria, which are usually used for chromosomal aberration testing with CHL, were employed. Appearance incidence of cell with chromosomal aberrations: Negative(-): less than 5% Equivocal(±): 5% or more, less than 10% Positive(+): 10% or more |

***Statistics***

|  |
| --- |
| No |

**Results and discussions**

**Test results**

|  |  |
| --- | --- |
| **Species/strain** | other: Chinese hamster lung (CHL/IU) cells |
| **Metabolic activation** | with and without |
| **Test system** | strain/cell type: Chinese hamster lung (CHL/IU) cells |
| **Genotoxicity** | negative |
| **Cytotoxicity** | no |
| **Vehicle controls valid** | yes |
| **Negative controls valid** | not examined |
| **Positive controls valid** | yes |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| [Continuous treatment] See Table 1  24 hr exposure: structure aberrations, polyploidy; Negative  48 hr exposure: structure aberrations, polyploidy; Negative  [Short-term treatment] See Table 2  -S9: structure aberrations, polyploidy; Negative  +S9: structure aberrations, polyploidy; Negative  Table 1. Chromosomal aberration test on CHL cells treated with 1,1,1 -tris(hydroxymethyl)ethane (continuous exposure)   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/mL) | Time of exposure  (hr) | Number of cells analyzed | Number of cells with structural aberration | | | | | | Total  [+gap]  (%) | Total  [-gap]  (%) | Polyploid cells  (%) | Final judgement | | | gap | ctb | csb | cte | cse | oth | SA | Pol | | Test sub. | 0 | 24 | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | - | - | |  | 300 | 24 | 200 | 0 | 0 | 0 | 1 | 0 | 0 | 0.5 | 0.5 | 0.5 | - | - | |  | 600 | 24 | 200 | 1 | 1 | 0 | 0 | 0 | 0 | 1.0 | 0.5 | 1.0 | - | - | |  | 1200 | 24 | 200 | 0 | 3 | 0 | 1 | 0 | 0 | 2.0 | 2.0 | 1.0 | - | - | | MMC\* | 0.05 | 24 | 200 | 15 | 30 | 1 | 66 | 0 | 0 | 43.5 | 41.5 | 0.5 | + | - | | Test sub. | 0 | 48 | 200 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 | 0.0 | 1.0 | - | - | |  | 300 | 48 | 200 | 1 | 0 | 0 | 1 | 0 | 0 | 1.0 | 0.5 | 1.0 | - | - | |  | 600 | 48 | 200 | 3 | 0 | 1 | 2 | 0 | 0 | 3.0 | 1.5 | 0.0 | - | - | |  | 1200 | 48 | 200 | 0 | 1 | 0 | 0 | 0 | 0 | 0.5 | 0.5 | 0.0 | - | - | | MMC\* | 0.025 | 48 | 200 | 15 | 22 | 0 | 73 | 0 | 0 | 44.0 | 40.5 | 1.0 | + | - |   \*:Positive control (mitomycin C)  ctb: chromatid break csb: chromosome break cte:chromatid exchange cse: chromosome exchange oth: others  SA: structural aberration Pol: polyploid cell  Table 2. Chromosomal aberration test on CHL cells treated with 1,1,1 -tris(hydroxymethyl)ethane (short-term exposure)   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Compound | Dose  (μg/mL) | S9  mix | Time of exposure  (hr) | Number of cells analyzed | Number of cells with structural aberration | | | | | | Total  [+gap]  (%) | Total  [-gap]  (%) | Polyploid cells  (%) | Final judgement | | | gap | ctb | csb | cte | cse | oth | SA | Pol | | Test sub. | 0 | - | 6 | 200 | 1 | 1 | 0 | 0 | 1 | 0 | 1.5 | 1.0 | 1.0 | - | - | |  | 300 | - | 6 | 200 | 1 | 1 | 0 | 2 | 0 | 0 | 1.5 | 1.0 | 0.5 | - | - | |  | 600 | - | 6 | 200 | 1 | 1 | 1 | 1 | 0 | 0 | 1.0 | 0.5 | 1.0 | - | - | |  | 1200 | - | 6 | 200 | 1 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.0 | 1.5 | - | - | | CP\* | 12.5 | - | 6 | 200 | 2 | 0 | 0 | 0 | 0 | 0 | 1.0 | 0.0 | 0.5 | - | - | | Test sub. | 0 | + | 6 | 200 | 0 | 0 | 0 | 1 | 0 | 0 | 0.5 | 0.5 | 0.0 | - | - | |  | 300 | + | 6 | 200 | 0 | 0 | 0 | 2 | 0 | 0 | 1.0 | 1.0 | 1.0 | - | - | |  | 600 | + | 6 | 200 | 1 | 0 | 0 | 2 | 0 | 0 | 1.5 | 1.0 | 0.0 | - | - | |  | 1200 | + | 6 | 200 | 1 | 2 | 0 | 2 | 0 | 0 | 2.0 | 2.0 | 1.0 | - | - | | CP\* | 12.5 | + | 6 | 200 | 23 | 51 | 2 | 134 | 1 | 0 | 74.0 | 73.5 | 0.5 | + | - |   \*:Positive control (cyclophosphamide)  ctb: chromatid break csb: chromosome break cte:chromatid exchange cse: chromosome exchange oth: others  SA: structural aberration Pol: polyploid cell |

**Overall remarks, attachments**

**Overall remarks**

|  |
| --- |
| No increase in chromosomal aberrations was observed in the test with either the short-term treatment (-S9 and +S9) or continuous treatment. In vitro chromosomal aberration tests using cultured cells (CHL/IU) were conducted to assess the potential of 1,1,1 -tris(hydroxymethyl)ethane to induce chromosomal aberrations. 1,1,1-Tris(hydroxymethyl)ethane did not induce chromosomal aberrations in cultured cells under the conditions of this study. The positive control showed expected results. |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| 1,1,1-Tris(hydroxymethyl)ethane did not induce chromosomal aberrations in cultured cells in the in vitro non-bacterial test. |

**7.8 Toxicity to reproduction**

**7.8.1 Toxicity to reproduction**

***Endpoint study record: Toxicity to reproduction.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-aed536d3-8412-4f14-83f5-94e148e24ce9 |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:06 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,1,1-Tris(hydroxymethyl)ethane by Oral Administration in Rats. | Toxicity Testing Reports of Environmental Chemicals, Vol.6, 43-53 | Hatano Research Institute, Food and Drug Safety Center |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Cross-reference to same study**

|  |
| --- |
| 7.5.1 Repeated dose toxicity: oral: Repeated dose toxicity: oral.001 7.8.2 Developmental toxicity/teratogenicity: Developmental toxicity/teratogenicity.001 |

**Materials and methods**

**Test type**

|  |
| --- |
| screening |

**Limit test**

|  |
| --- |
| no |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) | yes (haematological and clinical chemistry examination in only males) |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: White solid - Analytical purity: 99.0% - Impurities (identity and concentrations): bis(2,2-dimethylol propyl)ether:0.1%, bis(2,2-dimethylol)propoxy methane: 0.3%, pentaerythritol: 0.3%, water: 0.14% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Test animals**

**Species**

|  |
| --- |
| rat |

**Strain**

|  |
| --- |
| Crj: CD(SD) |

**Sex**

|  |
| --- |
| male/female |

***Details on test animals and environmental conditions***

|  |
| --- |
| TEST ANIMALS - Source: Charles River Japan, Inc. Hino - Age at study initiation: 8 weeks old - Weight at study initiation: Male: 296.5 - 330.7 g Female: 195.0 - 223.1 g - Housing: Rats were housed individually, except during the acclimation, mating, and nursing periods. From day 14 of pregnancy to the day of sacrifice, individual dams and litters were reared in rat breeding cages with pulp chips as bedding. - Diet: Ad libitum - Water: Ad libitum - Acclimation period: 6 days ENVIRONMENTAL CONDITIONS - Temperature (°C): 24 ± 1 °C - Humidity (%): 50 - 65% - Air changes (per hr): Approximately 15 times/hr - Photoperiod (hrs dark / hrs light): 12 hrs dark / 12 hrs light |

**Administration / exposure**

**Route of administration**

|  |
| --- |
| oral: gavage |

**Vehicle**

|  |
| --- |
| other: Distilled water for injection |

***Details on exposure***

|  |
| --- |
| PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in distilled water for injection. VEHICLE - Justification for use and choice of vehicle: No data - Amount of vehicle (if gavage): 5 ml/kg bw - Lot/batch no. (if required): 9609CA produced by Hikari Pharmaceutical Co., Ltd. Dosing volume: 5 mL/kg Stability (test solutions): At least 8 days.  Storage condition of test solution: Stored in a refrigerator. |

**Details on mating procedure**

|  |
| --- |
| M/F ratio per cage: 1:1 Length of cohabitation: up to 14 days Proof of pregnancy: Vaginal plug or sperm in vaginal smear referred to day 0 of pregnancy. |

**Analytical verification of doses or concentrations**

|  |
| --- |
| yes |

**Duration of treatment / exposure**

|  |
| --- |
| (P)Males: 42 days including 14 days pre-mating period and the subsequent 28 days (P)Females: Days including 14 days pre-mating, mating and gestation periods and the days until day 3 of lactation |

**Frequency of treatment**

|  |
| --- |
| Daily |

**Doses / concentrations**

|  |  |
| --- | --- |
| 0, 100, 300 and 1000 mg/kg bw/day | |
| **Basis** | actual ingested |

**No. of animals per sex per dose**

|  |
| --- |
| 13 animals/sex/dose |

**Control animals**

|  |
| --- |
| yes, concurrent vehicle |

***Further details on study design***

|  |
| --- |
| - Dose selection rationale: A preliminary study was conducted to determine the doses to be employed. The substance was administered for 2 weeks. As a result, decrease in body weight was observed in both sexes at doses of 1000 mg/kg bw/day. Based on these results, the doses in the main study were determined to be 100, 300 and 1000 mg/kg bw/day. |

**Examinations**

***Parental animals: Observations and examinations***

|  |
| --- |
| CAGE SIDE OBSERVATIONS: Yes  - Time schedule: Daily BODY WEIGHT: Yes - Time schedule for examinations:  Male: Body weights were determined on days 1 (before dosing), 8, 15, 22, 29, 36, 42 and 43 (at autopsy) in males. Female: Body weights were determined on days 1 (before dosing), 8 and 15 in all females, on day 22 in some females, on days 0, 7, 14 and 20 of gestation in pregnant females, on days 0 and 4 (at autopsy) of lactation in females that delivered, and on day 25 (at autopsy) of gestation in females that had not delivered. FOOD CONSUMPTION: Yes - Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes - Time schedule for examinations:  Male: Food consumption was determined for the same days as measurement of body weight except the mating period in males.  Female: Food consumption was determined for the same days as measurement of body weight except the mating period in all females, for days 0-7, 7-14 and 14-20 of gestation in pregnant females, and for days 0-4 of lactation in females that delivered. FOOD EFFICIENCY: No WATER CONSUMPTION: No |

***Estrous cyclicity (Parental animals)***

|  |
| --- |
| Estrous cyclicity observation: No data |

***Sperm parameters (Parental animals)***

|  |
| --- |
| Parameters examined in P male parental generations: testes weight, epididymides weight |

***Litter observations***

|  |
| --- |
| PARAMETERS EXAMINED: The following parameters were examined in F1 offspring:  Number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, and weight gain. GROSS EXAMINATION OF DEAD PUPS: Yes, for external and internal abnormalities. |

***Postmortem examinations (Parental animals)***

|  |
| --- |
| SACRIFICE:  Male animals: Rats were euthanized by exsanguination under ether anesthesia on the day after the last administration.  Maternal animals: Rats were euthanized by exsanguination under ether anesthesia on day 4 of lactation. GROSS NECROPSY: Yes HISTOPATHOLOGY / ORGAN WEIGHTS:  - Histopathological examined organ: Male: Control and 1000 mg/kg bw/day groups: Brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder, testes and epididymides Female: Control and 1000 mg/kg bw/day groups: Brain, heart, thymus, liver, kidneys, spleen, adrenals, urinary bladder and uterus. Non-pregnant females: ovaries ORGAN WEIGHTS: Yes - Weighted organ: Male:  All groups of males: Thymus, liver, kidneys, testes and epididymides. Female:  All groups of females: Thymus, liver and kidneys. |

***Postmortem examinations (Offspring)***

|  |
| --- |
| SACRIFICE: The F1 pups were euthanized on PND 4 by exsanguination under ether anesthesia. GROSS NECROPSY: Yes |

***Statistics***

|  |
| --- |
| Statistical analyses were conducted using Bartlett’s test, one way ANOVA, Dunnett’s or Scheffe’s pair wise comparison test, Kruskal-Wallis rank sum test chi square test and Mann-Whitney U- test. |

***Reproductive indices***

|  |
| --- |
| Number of mated pairs Number of copulated pairs Number of pregnant females Number of pregnant females with live pups Duration of mating Gestation length Copulation index (%) = (Number of copulated pairs/Number of mated pairs) ×100 Fertility index (%) = (Number of pregnant animals/Number of animals with successful copulation) ×100 Gestation index (%) = (Number of females with live pups/Number of pregnant females) ×100 Number of corpora lutea Number of implantations Implantation index (%) = (Number of implantation sites/Number of corpora lutea) ×100 Number of pups born Number of stillborns Deliver index (%) = (Number of pups born/Number of implantations) ×100 |

***Offspring viability indices***

|  |
| --- |
| Number of live pups on day 0 of lactation Birth index (%) = (Number of live pups on day 0/Number of implantation sites) ×100 Live birth index (%) = (Number of live pups on day 0/Number of pups born) ×100 Pups weight on day 0 of lactation Sex ratio on day 0 of lactation Number of live pups on day 4 of lactation Pups weight on day 4 of lactation Sex ratio on day 4 of lactation Viability index = (Number of live pups on day 4 after birth/Number of live pups born) ×100 |

**Results and discussions**

**Effect levels**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Endpoint** | **Generation** | **Sex** | **Effect level** | **Based on** | **Basis for effect level / Remarks** |
| NOAEL | P | male/female | 1000 mg/kg bw/day (actual dose received) |  | No significant reproductive effects were found in parental animals treated with doses up to 1000 mg/kg bw/day. |

**Results of examinations: parental animals**

***Clinical signs (parental animals)***

|  |
| --- |
| no effects |

***Body weight and food consumption (parental animals)***

|  |
| --- |
| yes |

***Reproductive function: estrous cycle (parental animals)***

|  |
| --- |
| no data |

***Reproductive function: sperm measures (parental animals)***

|  |
| --- |
| no effects |

***Reproductive performance (parental animals)***

|  |
| --- |
| no effects |

***Organ weights (parental animals)***

|  |
| --- |
| no effects |

***Gross pathology (parental animals)***

|  |
| --- |
| no effects |

***Histopathology (parental animals)***

|  |
| --- |
| no effects |

***Details on results (parental animals)***

|  |
| --- |
| Body weight (PARENTAL ANIMALS) Decrease in body weight gain was observed in pregnant females in the 1000 mg/kg bw/day group at gestation period but the decrease was not considered reproductive toxicity. |

**Results of examinations: offspring**

***Viability (offspring)***

|  |
| --- |
| no effects |

***Clinical signs (offspring)***

|  |
| --- |
| no effects |

***Body weight (offspring)***

|  |
| --- |
| no effects |

***Sexual maturation (offspring)***

|  |
| --- |
| not examined |

***Organ weights (offspring)***

|  |
| --- |
| not examined |

***Gross pathology (offspring)***

|  |
| --- |
| no effects |

***Histopathology (offspring)***

|  |
| --- |
| not examined |

**Any other information on results incl. tables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1. Summary of reproductive performance in parental rats   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) | 0 | 100 | 300 | 1000 | | Number of mated pairs | 13 | 13 | 13 | 13 | | Number of copulated pairs | 13 | 13 | 13 | 13 | | Copulation index (%) | 100 | 100 | 100 | 100 | | Number of pregnant animals | 12 | 12 | 10 | 12 | | Fertility index (%) | 92.3 | 92.3 | 76.9 | 92.3 | | Pairing days until copulation | 2.6 ± 0.9 | 2.8 ± 2.0 | 2.5 ± 1.1 | 2.1 ± 0.6 | | Frequency of vaginal estrous | 1.0 ± 0.0 | 1.1 ± 0.3 | 1.0 ± 0.0 | 1.0 ± 0.0 |   Copulation index (%) = (number of copulated pairs/Number of mated pairs) x 100  Fertility index = (number of pregnant animals/Number of copulated pairs) x 100  Table 2. Summary of development of pups   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Dose (mg/kg bw/day) | 0 | 100 | 300 | 1000 | | Number of pregnant females | 12 | 12 | 10 | 12 | | Number of pregnant females with live pups | 12 | 12 | 10 | 12 | | Gestation index (%) | 100.0 | 100.0 | 100.0 | 100.0 | | Gestation length in days | 22.3 ± 0.5 (12) | 22.4 ± 0.5 (12) | 22.4 ± 0.5 (10) | 22.6 ± 0.5 (12) | | Number of corpora lutea | 17.5 ± 1.7 (12) | 18.2 ± 2.4 (12) | 16.0 ± 1.2 (10) | 16.3 ± 1.2 (12) | | Number of implantation sites | 16.5 ± 1.6 (12) | 16.0 ± 3.6 (12) | 14.5 ± 2.6 (10) | 15.0 ± 2.3 (12) | | Implantation index | 94.5 ± 6.0 (12) | 87.9 ± 17.0 (12) | 90.5 ± 14.9 (10) | 91.5 ± 10.0 (12) | |  |  |  |  |  | | Day 0 of lactation |  |  |  |  | | Number of pups born | 15.2 ± 1.9 (12) | 14.3 ± 3.6 (12) | 13.4 ± 2.8 (10) | 13.1 ± 3.1 (12) | | Delivery index(%) | 91.9 ± 6.6 (12) | 89.9 ± 12.2 (12) | 92.1 ± 6.8 (10) | 85.8 ± 14.0 (12) | | Number of live pups | 15.0 ± 2.0 (12) | 14.2 ± 3.6 (12) | 13.4 ± 2.8 (10) | 13.1 ± 3.1 (12) | | Birth index (%) | 90.9 ± 7.3 (12) | 88.9 ± 13.2 (12) | 92.1 ± 6.8 (10) | 85.8 ± 14.0 (12) | | Live birth index (%) | 98.8 ± 2.7 (12) | 98.8 ± 3.0 (12) | 100.0 ± 0.0 (10) | 100.0 ± 0.0 (12) | | Pups weight (g) |  |  |  |  | | Male | 6.1 ± 0.4 (12) | 6.6 ± 0.8 (12) | 6.6 ± 0.8 (10) | 6.6 ± 0.6 (11) | | Female | 5.9 ± 0.6 (12) | 6.2 ± 0.8 (12) | 6.2 ± 0.7 (10) | 6.3 ± 0.5 (12) | |  |  |  |  |  | |  |  |  |  |  | | Day 4 of lactation |  |  |  |  | | Number of live pups | 14.8 ± 2.1 (12) | 14.1 ± 3.7 (12) | 13.3 ± 2.7 (10) | 13.1 ± 3.1 (12) | | Viability index (%) | 98.2 ± 3.2 (12) | 99.2 ± 2.9 (12) | 99.4 ± 2.0 (10) | 100.0 ± 0.0 (12) | | Pups weight (g) |  |  |  |  | | Male | 9.3 ± 0.8 (12) | 10.4 ± 2.3 (12) | 10.9 ± 2.0 (10) | 10.5 ± 0.9\* (11) | | Female | 9.1 ± 1.1 (12) | 10.1 ± 2.1 (12) | 10.6 ± 1.6 (10) | 10.3 ± 1.0 (12) | | Sex ratio (male/female) on day 4 (%) | 0.76 (78/102) | 0.85 (78/92) | 0.97 (66/68) | 0.62 (60/97) |   Parenthesis indicates the number of litters evaluated.  \*: significant difference from control, p<0.05  Gestation index (%) = (Number of females with live pups/Number of pregnant females) x 100  Implantation index (%) = (Number of implantation sites/Number of corpora lutea) x 100  Deliver index (%) = (Number of pups born/Number of implantation sites) x 100  Birth index (%) = (Number of live pups on day 0/Number of implantation sites) x 100  Live birth index (%) = (Number of live pups on day 0/Number of pups born) x 100  Viability index (%) = (Number of live pups on day 4/Number of live pups on day 0) x 100 |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| No adverse effects were seen at the maximum tested oral dose of 1,000 mg/kg bw/day. The NOAEL for reproductive and developmental toxicity was therefore 1,000 mg/kg bw/day. |

**7.8.2 Developmental toxicity / teratogenicity**

***Endpoint study record: Developmental toxicity / teratogenicity.001***

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-bcdc9900-db41-4bbb-84e0-49c34226630d |
| **Dossier UUID** |  | 0 |
| **Author** |  | mariko / National Institute of Health Sciences / Tokyo / Japan |
| **Date** |  | 2011-12-01 10:23:06 JST |
| **Remarks** |  |  |

|  |  |
| --- | --- |
|  |  |

**Administrative Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose flag** | key study | | |
| **Study result type** | experimental result |  |  |
| **Reliability** | 1 (reliable without restriction) | | |
| **Rationale for reliability incl. deficiencies** | OECD Test Guideline study under GLP condition | | |

**Data source**

**Reference**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference type** | **Author** | **Year** | **Title** | **Bibliographic source** | **Testing laboratory** | **Report no.** | **Owner company** | **Company study no.** | **Report date** |
| study report | MHW (Ministry of Health and Welfare), Japan | 1998 | Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,1,1-Tris(hydroxymethyl)ethane by Oral Administration in Rats. | Toxicity Testing Reports of Environmental Chemicals, Vol.6, 43-53 | Hatano Research Institute, Food and Drug Safety Center |  |  |  |  |

**Data access**

|  |
| --- |
| data published |

**Cross-reference to same study**

|  |
| --- |
| 7.5.1 Repeated dose toxicity: oral: Repeated dose toxicity: oral.001 7.8.1 Toxicity to reproduction: Toxicity to reproduction.001 |

**Materials and methods**

**Limit test**

|  |
| --- |
| no |

**Test guideline**

|  |  |  |
| --- | --- | --- |
| **Qualifier** | **Guideline** | **Deviations** |
| according to | other guideline: OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) | yes (haematological and clinical chemistry examination in only males.) |

**GLP compliance**

|  |
| --- |
| yes |

**Test materials**

**Identity of test material same as for substance defined in section 1 (if not read-across)**

|  |
| --- |
| yes |

**Test material identity**

|  |  |
| --- | --- |
| **Identifier** | **Identity** |
| CAS number | 77-85-0 |

**Details on test material**

|  |
| --- |
| - Name of test material (as cited in study report): 1,1,1-Tris(hydroxymethyl)ethane - Physical state: White solid - Analytical purity: 99.0% - Impurities (identity and concentrations): bis(2,2-dimethylol propyl)ether:0.1%, bis(2,2-dimethylol)propoxy methane: 0.3%, pentaerythritol: 0.3%, water: 0.14% - Supplier: Mitsubishi Gas Chemical Company, Inc. - Lot/batch No.: 80913 - Storage condition of test material: Room temperature |

**Test animals**

**Species**

|  |
| --- |
| rat |

**Strain**

|  |
| --- |
| Crj: CD(SD) |

***Details on test animals and environmental conditions***

|  |
| --- |
| TEST ANIMALS - Source: Charles River Japan, Inc. Hino - Age at study initiation: 8 weeks old - Weight at study initiation: Male: 296.5 - 330.7 g Female: 195.0 - 223.1 g - Housing: Rats were housed individually, except during the acclimation, mating, and nursing periods. From day 14 of pregnancy to the day of sacrifice, individual dams and litters were reared in rat breeding cages with pulp chips as bedding. - Diet: Ad libitum - Water: Ad libitum - Acclimation period: 6 days ENVIRONMENTAL CONDITIONS - Temperature (°C): 24 ± 1 °C - Humidity (%): 50 - 65% - Air changes (per hr): Approximately 15 times/hr - Photoperiod (hrs dark / hrs light): 12 hrs dark / 12 hrs light |

**Administration / exposure**

**Route of administration**

|  |
| --- |
| oral: gavage |

**Vehicle**

|  |
| --- |
| other: Distilled water for injection |

***Details on exposure***

|  |
| --- |
| PREPARATION OF DOSING SOLUTIONS: Test substance was dissolved in distilled water for injection.  VEHICLE - Justification for use and choice of vehicle: No data - Amount of vehicle (if gavage): 5 ml/kg bw - Lot/batch no. (if required): 9609CA produced by Hikari Pharmaceutical Co., Ltd. Dosing volume: 5 mL/kg Stability (test solutions): At least 8 days.  Storage condition of test solution: Stored in a refrigerator. |

**Analytical verification of doses or concentrations**

|  |
| --- |
| yes |

**Details on mating procedure**

|  |
| --- |
| M/F ratio per cage: 1:1 Length of cohabitation: up to 14 days Proof of pregnancy: Vaginal plug or sperm in vaginal smear referred to day 0 of pregnancy. |

**Duration of treatment / exposure**

|  |
| --- |
| (P)Males: 42 days including 14 days pre-mating period and the subsequent 28 days (P)Females: Days including 14 days pre-mating, mating and gestation periods and the days until day 3 of lactation |

**Frequency of treatment**

|  |
| --- |
| Daily |

**Doses / concentrations**

|  |  |
| --- | --- |
| 0, 100, 300 and 1000 mg/kg bw/day | |
| **Basis** | actual ingested |

**No. of animals per sex per dose**

|  |
| --- |
| 13 animals/sex/dose |

**Control animals**

|  |
| --- |
| yes, concurrent vehicle |

***Further details on study design***

|  |
| --- |
| - Dose selection rationale: A preliminary study was conducted to determine the doses to be employed. The substance was administered for 2 weeks. As a result, decrease in body weight was observed in both sexes at doses of 1000 mg/kg bw/day. Based on these results, the doses in the main study were determined to be 100, 300 and 1000 mg/kg bw/day. |

**Examinations**

***Maternal examinations***

|  |
| --- |
| CAGE SIDE OBSERVATIONS: Yes  - Time schedule: Daily BODY WEIGHT: Yes - Time schedule for examinations:  Body weights were determined on days 1 (before dosing), 8 and 15 in all females, on day 22 in some females, on days 0, 7, 14 and 20 of gestation in pregnant females, on days 0 and 4 (at autopsy) of lactation in females that delivered, and on day 25 (at autopsy) of gestation in females that had not delivered. FOOD CONSUMPTION: Yes - Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes - Time schedule for examinations:  Female: Food consumption was determined for the same days as measurement of body weight except the mating period in all females, for days 0-7, 7-14 and 14-20 of gestation in pregnant females, and for days 0-4 of lactation in females that delivered. FOOD EFFICIENCY: No WATER CONSUMPTION: No |

***Ovaries and uterine content***

|  |
| --- |
| The ovaries and uterine content was examined after termination: Yes Examinations included: - Gravid uterus weight: No - Number of corpora lutea: Yes - Number of implantations: Yes - Number of early resorptions: No data - Number of late resorptions: No data |

***Fetal examinations***

|  |
| --- |
| The following parameters were examined for development of F1 offspring:  Body weight, postnatal mortality, presence of gross anomalies |

***Indices***

|  |
| --- |
| Body weight of live pups on birthday and on day 4 after birth Viability index (=(Number of live pups on day 4 after birth/Number of live pups born) ×100) Number of external anomalies |

**Results and discussions**

**Effect levels**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endpoint** | **Effect type** | **Effect level** | **Based on** | **Basis for effect level / Remarks** |
| NOAEL | developmental toxicity | 1000 mg/kg bw/day (actual dose received) |  | The test substance showed no effects in the developmental toxicity test |

***Maternal toxic effects***

|  |
| --- |
| yes |

***Details on maternal toxic effects***

|  |
| --- |
| Decrease in body weight gain was observed in pregnant females in the 1000 mg/kg bw/day group at gestation period but the decrease was not considered reproductive toxicity. |

**Embryotoxic / teratogenic effects**

|  |
| --- |
| no effects |

**Applicant's summary and conclusion**

**Conclusions**

|  |
| --- |
| No adverse effects were seen at the maximum tested oral dose of 1,000 mg/kg bw/day. The NOAEL for reproductive and developmental toxicity was therefore 1,000 mg/kg bw/day. |

**Reference substance: 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl-**

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC5-3306ca57-7e96-4ef8-a4d6-dcf703b6501d |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-14 20:53:20 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

**General information**

|  |  |
| --- | --- |
| **Reference substance name** | 1,3-Propanediol, 2-(hydroxymethyl)-2-methyl- |

**EC inventory**

|  |  |  |  |
| --- | --- | --- | --- |
| **EC number** | 201-063-9 | **CAS number** | 77-85-0 |
| **EC name** | ethylidynetrimethanol | | |
| **Molecular formula** | C5H12O3 | | |

**Reference substance information**

**CAS information**

|  |  |
| --- | --- |
| **CAS number** | 77-85-0 |
| **CAS name** | 1,1,1-Tris(hydroxymethyl)ethane |

**Molecular and structural information**

|  |  |
| --- | --- |
| **Molecular formula** | C5H12O3 |

**Legal entity: National Institute of Health Sciences**

|  |  |  |
| --- | --- | --- |
| **UUID** |  | IUC4-b036ff75-0f3c-323b-b200-ed5f46cf5101 |
| **Dossier UUID** |  | 0 |
| **Author** |  | XML Transformation V2.0 Plug-In |
| **Date** |  | 2011-06-23 11:55:01 JST |
| **Remarks** |  | Successfully migrated to IUCLID 5.3 format. |

**General information**

|  |  |
| --- | --- |
| **Legal entity name** | National Institute of Health Sciences |

**Identifiers**

**Other IT system identifiers**

|  |  |  |  |
| --- | --- | --- | --- |
| **Flags** | **IT system** | **ID** | **Remarks** |
|  | LEO | 10767 |  |
|  | IUCLID4 | 16558402024DIV750 |  |

**Contact information**

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| **Country** | Japan |

**Contact persons**

|  |  |
| --- | --- |
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| **Title** | Dr. |
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| **Country** | Japan |