SCREENING-LEVEL HAZARD CHARACTERIZATION

1,3-Pentanediol, 2,2,4-trimethyl- (CASRN 144-19-4)

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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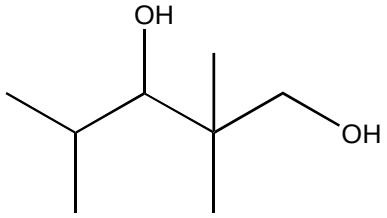
[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**144-19-4**
Chemical Abstract Index Name	**1,3-Pentanediol, 2,2,4-trimethyl-**
Structural Formula	

Summary

CASRN 144-19-4 is a white, crystalline solid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of CASRN 144-19-4 is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 144-19-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of CASRN 144-19-4 is low in rats, mice, and guinea pigs via the oral route and low in rats via the inhalation route. Following repeated dietary administration of CASRN 144-19-4 to rats for 57 days, mean absolute and relative liver, kidney and adrenal gland weights were significantly higher and mean absolute lung weights were significantly lower for male rats at 1000 mg/kg/day. At the same dose, mean absolute and relative liver and adrenal gland weights and relative kidney, heart and brain weights were significantly higher for female rats. Although there is no histopathological correlation to organ weight changes, the NOAEL for systemic toxicity is 250 mg/kg/day. A single-dose three-generation reproduction toxicity study in rats exposed via the diet to ~ 500 mg/kg/day CASRN 144-19-4 showed significantly higher pup mortality rates for treated litters from three generations and significantly decreased pup weights for litters from one of two F1 generations, and for litters from one of two F2 generations; the NOAEL for reproductive/developmental toxicity was not established. No maternal toxicity was observed; the NOAEL for maternal toxicity is ~500 mg/kg/day (only dose tested). CASRN 144-19-4 was not mutagenic in an *in vitro* bacterial reverse mutation assay and did not induce chromosomal aberrations in mammalian cells *in vitro*.

The 96-h LC_{50} for fish exposed to CASRN 144-19-4 is > 700 mg/L. The 48-h EC_{50} for aquatic invertebrates exposed to CASRN 144-19-4 is >109.1 mg/L. The 72-h EC_{50} for aquatic plants from exposure to CASRN 144-19-4 is >110.1 mg/L (biomass and growth).

No data gaps were identified under the HPV Challenge Program.

The sponsor, Eastman Chemical Company, submitted a Test Plan and Robust Summaries to EPA for 1,3-Pentanediol, 2,2,4-trimethyl- (CAS No. 144-19-4; 9th CI name: 1,3-pentanediol, 2,2,4-trimethyl-) on March 26, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on April 19, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/24trimlp/c13674tc.htm). EPA comments on the original submission were posted to the website on August 20, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 15, 2002, which were posted to the ChemRTK website on September 20, 2002.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2002 Test Plan and Robust Summary. CASRN 144-19-4 is a solid, white, crystalline material. Test substance purity for many of the studies in the Robust Summary was not available. When the test substance purity was noted in the Robust Summary, it was given as 99%.

1.2. Physical-Chemical Properties

The physical-chemical properties of CASRN 144-19-4 are summarized in Table 1.

Table 1 Physical-Chemical Properties of 1,3-Pentanediol, 2,2,4-trimethyl-[1]

Property	Value
CASRN	144-19-4
Molecular Weight	146.23
Physical State	Solid, white crystalline
Melting Point	51.5°C (measured)
Boiling Point	232 °C at 760 mmHg (measured)[2]
Vapor Pressure	0.0045 mm Hg at 25°C (measured)[2]
Water Solubility	19,000 mg/L at 25°C (measured)
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	4.6×10^{-8} atm-m^3/mole (estimated)[3]
Log K_{ow}	1.24 (measured)[2]

[1] Eastman Chemical Company. September 9, 2002. Revised Robust Summary and Test Plan for 2,2,4-Trimethylpentane-1,3-diol. Available online from: http://www.epa.gov/chemrtk/pubs/summaries/24trimlp/c13674tc.htm. As of June 8, 2010.

[2] SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.srcinc.com/what-we-do/free-demos.aspx as of July 1, 2010.

[3] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm. As of July 1, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 144-19-4 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as intermediates and solvents which become part of product formulation or mixture. Non-confidential commercial and consumer uses of this chemical include paints and coatings.

2.2. Environmental Exposure and Fate

The environmental fate properties of CASRN 144-19-4 are summarized in Table 2.

1,3-Pentanediol, 2,2,4-trimethyl- is expected to have high mobility in soil. 1,3-Pentanediol, 2,2,4-trimethyl- was readily biodegradable using the modified AFNOR test (OECD 301A), achieving 99 and 100% biodegradation in two separate tests as measured by dissolved organic content (DOC). Another biodegradation study indicated mixed results with 1,3-pentanediol, 2,2,4-trimethyl- reaching 4, 5, and 82% theoretical biochemical oxygen demand (BOD) using the modified MITI test (OECD 301C), but the compound was classified as not readily biodegradable due to the inconsistency in the results. These data suggest that substantial biodegradation of 1,3-pentanediol, 2,2,4-trimethyl- can occur under optimal conditions. The rate of hydrolysis is expected to be negligible since this substance does not possess labile functional groups that hydrolyze under environmental conditions. The rate of volatilization is considered low based on its Henry's Law constant. 1,3-Pentanediol, 2,2,4-trimethyl- is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of 1,3-Pentanediol, 2,2,4-trimethyl-[1]	
Property	**Value**
Photodegradation Half-life	7.3 hours at 25°C (estimated)[2]
Hydrolysis Half-life	Stable
Biodegradation	99 and 100% biodegradation in 28 days (readily biodegradable) 4, 5, and 82% biodegradation in 28 days (not readily biodegradable)[3]
Bioaccumulation Factor	BCF = 0.6–0.8 (measured in carp at 1 mg/L)[3] BAF = 2.0 (estimated)[2]
Log K_{oc}	0.3 (estimated)[2]
Fugacity (Level III Model)[2]	
Air (%)	0.66
Water (%)	40.2
Soil (%)	59.1
Sediment (%)	<0.1
Persistence[4]	P1 (low)
Bioaccumulation[4]	B1 (low)

[1] Eastman Chemical Company. 2002. Revised Robust Summary and Test Plan for 2,2,4-Trimethylpentane-1,3-diol. Available online from: http://www.epa.gov/chemrtk/pubs/summaries/24trimlp/c13674tc.htm as of July 1, 2010.
[2] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 1, 2010.
[3] National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of July 1, 2010.
[4] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: 1,3-Pentanediol, 2,2,4-trimethyl- is a white, crystalline solid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of 1,3-pentanediol, 2,2,4-trimethyl- is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. 1,3-Pentanediol, 2,2,4-trimethyl- is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

1) Rats (1/dose, gender and strain not specified) were dosed with 400, 800, 1600, 3200 or 6400 mg/kg-bw of the test substance by oral gavage and monitored for 14 days. Animals from the three highest doses died within 1 hour of test substance administration.
ALD ~ 800 – 1600 mg/kg-bw

(2) Mice (1/dose, gender and strain not specified) were dosed with 200, 400, 800, 1600 or 3200 mg/kg-bw of the test substance by oral gavage and monitored for 14 days. The animal from the highest dose died within 20 minutes of test substance administration; no other mortalities were reported.
ALD ~ 1600 – 3200 mg/kg-bw

(3) Rats (4/sex/dose, strain not specified) were dosed with 3000, 4000, 5000, 6000 or 7000 mg/kg-bw of the test substance by oral gavage and monitored for 14 days. All rats except for one rat from the 3000 mg/kg-bw group died by day 2.
LD_{50} < 3000 mg/kg-bw

(4) Male mice (6/dose, strain not specified) were dosed with the test substance by oral gavage at doses of 1000, 1500, 1800, 2200, 2600, 3100 or 3700 mg/kg-bw and observed for 14-days. Animals from the 2600, 3100 and 3700 mg/kg groups died within 3 days of treatment.
LD_{50} ~ 2200 mg/kg-bw

(5) Male guinea pigs (6/dose, strain not specified) were dosed with the test substance by oral gavage at doses of 1000, 1500, 1800, 2200, 2600 and 3100 mg/kg-bw and observed for 14 days. All animals from the 2600 and 3100 mg/kg-bw groups and approximately half of the animals from the 1800 and 2200 mg/kg-bw groups died by Day 1 of the study.
LD_{50} = 1800 mg/kg-bw

Acute Inhalation Toxicity

Rats (4/sex, strain not specified) were exposed to the test substance at a concentration of 4.5 mg/L for 6 hours. No mortality was observed.
LC_{50} > 4.5 mg/L

Repeated-Dose Toxicity

In a 60-day study, CFE rats (15/sex for treatment groups, 60 controls) were treated with 0, 0.5, 1.0 or 2% of the test substance (approximately 0, 250, 500 or 1000 mg/kg/day) in feed for 30 days. At the end of 30 days, all animals from the 1.0% treatment group and 15 animals from the control group were used for a fertility study and the remaining animals exposed for a further 27 days. A single female rat from the high dose group and two male rats from the control group died; however, the deaths were attributed to laboratory accidents. Mean body weight gains and food consumption were significantly reduced in high dose females and slightly reduced in high-dose males. There were no effects observed in hematology or clinical chemistry parameters, or from gross/microscopic examinations of organs. Mean absolute and relative liver, kidney and adrenal gland weights were significantly higher for male rats from the high dose group and mean absolute lung weights were significantly lower for male rats from the high- and low-dose groups (there was no effect on the lung body weight ratio). Mean absolute and relative liver and adrenal gland weights and relative kidney, heart and brain weights were significantly higher for female rats in the high dose group. The mean relative lung weight was significantly lower for female

rats from the low dose group (absolute values were normal) There were no histopathological changes seen in the organs..
LOAEL ~ 1000 mg/kg-bw/day (based on weight changes in multiple organs, including significantly increased absolute and relative liver, kidney and adrenal weights for male rats and significantly higher absolute and relative liver and adrenal gland weights and relative kidney, heart, and brain weights for female rats)
NOAEL ~ 250 mg/kg/day

Reproductive/Developmental Toxicity

Rats (15/sex/group, strain not reported) received either control feed or 1% test substance (approximately 500 mg/kg/day) in feed for three generations. The F0 parental generation was treated for 30 days prior to being started on study. These rats were mated twice to yield an F1a and F1b generation. The F1a animals were also allowed to mate twice to create an F2a and F2b generation, and the F2a animals were used to generate an F3a and F3b generation. Mortality in F3a pups required a third mating with F2a animals to yied an F3c generation. The summary did not provide any information on the duration of exposures for any of these scenarios (premating, mating, gestation or lactation, or when pups began treatment for successive generations) except to state that "all animals were maintained on their assigned diets throughout the entire study". The percentage of inseminations and pregnancies and the average gestation period and litter size were comparable among treated and control groups. Pup mortality rates from birth to 2 weeks post weaning were erratic across generations. Treated litters from three generations (F1b, F2a, and F3a) had significantly higher mortality rates than the control group; treated litters from two generations (F1a, F3b) had mortality rates that were comparable to the control group; and treated litters from one generation (F2b) had a significantly lower mortality rate than the control group. Mean pup body weights were significantly lower for litters from one of two F1 generations at 2 weeks post-weaning and for litters from one of two F2 generations from weaning to necropsy (7 – 9 weeks of age); maternal toxicity was not observed at this dose level. No gross lesions or developmental effects were observed at necropsy.
LOAEL (reproductive/developmental toxicity) ~ 500 mg/kg/day (based on pup mortality and lower pup body weights at the only dose tested).
NOAEL (reproductive/developmental toxicity) = Not established
NOAEL (maternal) ~ 500 mg/kg/day (only dose tested)

Genetic Toxicity – Gene Mutation

In vitro
Salmonella typhimurium (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* WP2uvrA were exposed to concentrations (number and values not provided) of the test substance of up to 5000 μg/plate with and without metabolic activation. No evidence of precipitation or cytotoxicity was observed at the highest concentration used (5000 μg/plate) and no positive responses were induced by the test compound. Positive controls (benzo[a]pyrene, 2-aminoanthracene, 2-nitrofluorene, sodium azide, 2-aminoanthracene, ICR-191 and 4-nitroquinoline-N-oxide) and negative controls (DMSO) were run concurrently, but results were not provided.
CASRN 144-19-4 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary (CHO) cells were exposed to test substance concentrations of between 10.2 and 1500 μg/mL, with and without metabolic activation. Positive controls (mitomycin-C and cyclophosphamide) and negative controls (water) were tested concurrently, but results were not provided. No cytotoxicity or precipitation was observed at the highest concentration tested. No significant increases in cells with chromosomal aberrations, polyploidy or endoreduplication were observed.

CASRN 144-19-4 did not induce chromosomal aberrations in this assay.

Conclusion: The acute toxicity of CASRN 144-19-4 is low in rats, mice, and guinea pigs via the oral route and low in rats via the inhalation route. Following repeated dietary administration of CASRN 144-19-4 to rats for 57 days, mean absolute and relative liver, kidney and adrenal gland weights were significantly higher and mean absolute lung weights were significantly lower for male rats at 1000 mg/kg/day. At the same dose, mean absolute and relative liver and adrenal gland weights and relative kidney, heart and brain weights were significantly higher for female rats. Although there is no histopathological correlation to organ weight changes, the NOAEL for systemic toxicity is 250 mg/kg/day. A single-dose three-generation reproduction toxicity study in rats exposed via the diet to ~ 500 mg/kg/day CASRN 144-19-4 showed significantly higher pup mortality rates for treated litters from three generations and significantly decreased pup weights for litters from one of two F1 generations, and for litters from one of two F2 generations; the NOAEL for reproductive/developmental toxicity was not established. No maternal toxicity was observed; the NOAEL for maternal toxicity is ~500 mg/kg/day (only dose tested). CASRN 144-19-4 was not mutagenic in an *in vitro* bacterial reverse mutation assay and did not induce chromosomal aberrations in mammalian cells *in vitro*.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data	
Endpoint	**SPONSORED CHEMICAL 1,3-Pentanediol, 2,2,4-trimethyl- (144-19-4)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**1800-3000**
Acute Inhalation Toxicity LC_{50} (mg/L)	**> 4.5**
Repeated-Dose Toxicity (NOAEL/LOAEL) Oral (mg/kg/day)	**NOAEL ~ 250 LOAEL ~ 1000**
Reproductive Toxicity (NOAEL/LOAEL) Oral (mg/kg/day)	**NOAEL = not established LOAEL ~ 500**
Developmental Toxicity (NOAEL/LOAEL) Oral (mg/kg/day)	
Maternal Toxicity	**NOAEL ~ 500 (only dose tested)**
Developmental Toxicity	**NOAEL = not established LOAEL ~ 500**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**

Measured data in bold text

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Bluegill sunfish (*Lepomis macrochirus)* were exposed to CASRN 144-19-4 at nominal test concentrations of 0, 91, 150, 250, 420 and 700 mg/L for 96 hours under static exposure conditions. CASRN 144-19-4 was dissolved in acetone and a solvent control was included in the study design. Twenty-percent mortality was observed at the highest dose concentration (700 mg/L). Control survival was 100%.

96-h LC_{50} > 700 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna* (10/group)) were exposed to CASRN 144-19-4 at nominal concentrations of 0 or 110 mg/L under static exposure conditions. The measured concentration of the test substance was 109.1 mg/L. No immobilization was observed during the study in the control or treated groups.
48-h EC_{50} > 109.1 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 144-19-4 at nominal concentrations of 0 or 110 mg/L under static exposure conditions. The measured test substance concentration was 110.1 mg/L. No effects on biomass or growth rate were observed.
72-h EC_{50} (biomass) > 110.1 mg/L
72-h EC_{50} (growth) > 110.1 mg/L

Conclusion: The 96-h LC_{50} for fish exposed to CASRN 144-19-4 is > 700 mg/L. The 48-h EC_{50} for aquatic invertebrates exposed to CASRN 144-19-4 is >109.1 mg/L. The 72-h EC_{50} for aquatic plants from exposure to CASRN 144-19-4 is >110.1 mg/L (biomass and growth).

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data

Endpoint	SPONSORED CHEMICAL 1,3-Pentanediol, 2,2,4-trimethyl- (144-19-4)
Fish 96-h LC_{50} (mg/L)	**> 700**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**> 109.1**
Aquatic Plants 72-h EC_{50} (mg/L)	
(Growth)	**> 110.1**
(Biomass)	**> 110.1**

bold = measured data (i.e., derived from testing)