FOREWORD INTRODUCTION

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate

CAS N°:6846-50-0

SIDS Initial Assessment Report

For

SIAM 3

Williamsburg, Virginia, 13-15 February 1995

1. Chemical Name: 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate

2. CAS Number: 6846-50-0

3. Sponsor Country: Japan
National SIDS Contact Point:
Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs

4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium
- Process used

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

As a high priority chemical for initial assessment, 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was selected in the framework of the OECD HPV Chemicals Programme. SIDS Dossier and Testing Plan were reviewed at a SIDS Review Meeting in 1993, where the following SIDS Testing Plan was agreed.

No testing ( )
Testing (X)
Physical-Chemical Properties
Melting point
Vapour pressure
Partition coefficient
Water solubility
Environmental fate/Biodegradation
Biodegradation
Photodegradation
Stability in water
Ecotoxicity
Acute toxicity to fish
Acute toxicity to daphnids
Toxicity to algae
Chronic toxicity to daphnids

Toxicity

Repeated dose toxicity
Reproductive toxicity
Gene mutation
Chromosomal aberration

At SIAM-2, the conclusions were approved with comments.
Comments at SIAM-2: Rearrangement of the documents.

7. Review Process Prior to the SIAM:

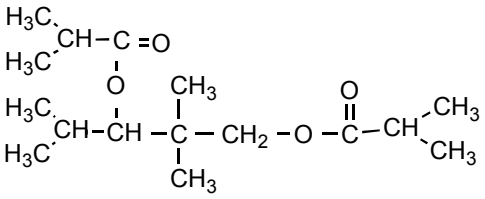
8. Quality check process:

9. Date of Submission: December 1994

10. Date of last Update:

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6846-50-0
Chemical Name	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is stable liquid and the production volume is ca. 1,200 tonnes/year in 1990 - 1993 in Japan. This chemical is used as additives to plastic (plasticizer). This chemical is stable in neutral and acidic solutions, and is considered as “inherently biodegradable”.

PECs have been calculated based on an emission and effluent scenario and a dilution factor. $PECs_{local}$ for the aquatic compartment were 5.1×10^{-11} and 1.3×10^{-8} mg/l.

For the environment, various NOEC and LC_{50} values were gained from test results; LC_{50} = 18 mg/l (acute fish); EC_{50} = 300 mg/l (acute daphnia); EC_{50} = 8.0 mg/l (acute algae); NOEC = 5.3 mg/l (acute algae); NOEC = 3.2 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be moderately toxic to algae and daphnids, and slightly toxic to fish. The lowest chronic toxicity data to daphnia, 21d-NOEC (reproduction) of *Daphnia magna* (3.2 mg/l) was adopted for the calculation of PNEC. An assessment factor of 100 was used to both acute and chronic toxicity data to determine PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, PNEC of the chemical is 0.032 mg/l. The PEC is lower than the PNEC, therefore the environmental risk is presumably low.

Neither monitoring data at work place nor consumer exposure have been reported. Based on the physico-chemical properties and a calculation model, the level exposed indirectly through the environment was estimated as 9.3×10^{-4} mg/man/day. . The daily intake through drinking water is estimated as 4.2×10^{-7} mg/kg/day and through fish is calculated as 1.5×10^{-5} mg/kg/day.

The chemical showed no genotoxic effects in bacteria and chromosomal aberration test *in vitro*.

In a combined repeat dose and reproductive/developmental toxicity screening test, increase of liver and kidney weights were observed in parental animals from the middle dose level (150 mg/kg/day). In the histopathological examinations, increases in grade of basophilic change of renal tubular epithelium and degeneration of hyaline droplet were observed from the same level. In addition, necrosis and other renal effects were also observed. From the view point of reproductive/developmental end-points, there were no effects observed related to mating, fertility and oestrus cycle and also for dams during the pregnancy and lactation period and for pups after their birth. Therefore, NOEL was 30 mg/kg/day for repeated dose toxicity as well as 750 mg/kg/day for reproductive toxicity.

As for indirect exposure via the environment, the daily intake through drinking water is estimated as 4.2×10^{-7} mg/kg/day and through fish is calculated as 1.5×10^{-5} mg/kg/day. The margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and

exposure situation.

In conclusion, no further testing is needed at present considering its toxicity and exposure levels.

NATURE OF FURTHER WORK RECOMMENDED

FULL SIDS SUMMARY

CAS NO: 6846-50-0		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			< -10 °C
2.2	Boiling Point			280 °C at 1,013 hPa
2.3	Density			No data available
2.4	Vapour Pressure		OECD TG 104	8.8 x 10^{-2} Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	> 4.11 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	15 mg/l at 25 °C
B.	pH			No data available.
	pKa			No data available
2.12	Oxidation: Reduction Potential			No data available.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			Half-life: 90.7 years
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4.0 and 7.0. Half-life: 178 days at pH 9.
3.2	Monitoring Data			No data available
3.3	Transport and Distribution		Calculated (Fugacity Level III)	100% released to water, In Air 3.4E-10 mg/l In Water 1.2E-05 mg/l In Soil 7.4E-06 mg/kg In Sediment 3.2E-03 mg/kg
3.5	Biodegradation		OECD TG 301C	Inherently biodegradable: 4-82 % (BOD) in 28 days, 2-84% (TOC), 3-100 % (GC) in 28 days
3.6	Bioaccumulation	Carp	OECD TG 305C	BCF: 5.2 – 31
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (24hr): 18 mg/L LC_{50} (96hr): 18 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24hr): 300 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr): 8.0 mg/l NOEC: 5.3 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Mortality): 12 mg/l EC_{50} (14d, Reproduction): 5.6 mg/l NOEC (21d, Repro): 3.2 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No data available.
4.6.2	Toxicity to Terrestrial Plants			No data available.

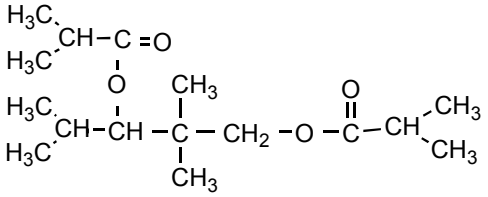
CAS NO: 6846-50-0		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	$LD_{50:}$ > 3,200 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Unknown	453 ppm/6H
5.1.3	Acute Dermal Toxicity	Guinea pig	Unknown	LD_{50}: > 20 ml/kg
5.4	Repeated Dose Toxicity	Rat	OECD Combined Test	NOAEL = 30 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. .typhimurium* *E. coli*	OECD TG 471 and 472 and Japanese Guidelines	Negative (With and without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL cells	OECD TG 473 and Japanese Guidelines	Negative (With metabolic activation) Negative (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data available
5.8	Toxicity to Reproduction	Rat	OECD Combined Test	NOAEL Parental = 750 mg/kg/day NOAEL F1 offspring = 750 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			
5.11	Experience with Human Exposure			

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 6846-50-0
Chemical Name: 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
Molecular Formula: $C_{16}H_{30}O_4$
Structural Formula:



1.2 Purity/Impurities/Additives

Degree of Purity: > 99 %

Major Impurities: 2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate

Essential Additives: No additives

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Melting point	< -10 °C
Boiling point	280 °C
Vapour pressure	8.8 x 10^{-2} Pa at 25 °C
Water solubility	15 mg/l
Partition coefficient n-octanol/water (log value)	> 4.11

2 GENERAL INFORMATION ON EXPOSURE

2.1 General discussion

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a stable liquid and the production volume is ca. 1,200 tonnes/year in 1990 - 1993 in Japan. This chemical is used as an additive for plastic (plasticizer). All disposal wastes are treated by incineration. The chemical seems to be released into water and air from its production sites after biological treatment. No specific monitoring data of the chemical is available. This chemical is stable in neutral and acidic solutions, and is considered to be “inherently biodegradable”.

2.2 Environmental exposure

2.2.1 Biodegradability:

If released into water, this substance is inherently biodegraded (MITI (I), corresponding to the OECD 301C: 4-82 % during 28 days based on BOD and 2-84 % based on TOC and 3-100 % based on GC analysis).

2.2.2 Hydrolysis as a function to pH:

The chemical is stable in water at pH 4 and 7 (OECD TG 111). The half-life at pH 9 is 178 days.

2.2.3 Photodegradability (estimation)

A half-life time of 90.7 years is estimated for the direct photodegradation of the chemical in water (MITI, Japan).

2.2.4 Bioaccumulation:

BCF= 5.2 – 31 in carp (6 weeks at 25 °C) suggests that the potential for bioconcentration in aquatic organisms is low.

2.2.5 Estimates of environmental fate, pathway and concentration:

Global situation:

Method: MNSEM 147S (Details are shown in Form-1 Annex)
Input data:

Molecular weight:	286.41
Water solubility:	10.00 [mg/l]
Vapor pressure:	7.5E-04 [mmHg]
Log Pow:	4.32

Results: Steady state mass and concentration calculated using MNSEM 147S

Air:	3.4E-10 [mg/l]
Water:	1.2E-05 [mg/l]
Soil:	7.4E-06 [mg/kg dry solid]
Sediment:	3.2E-03 [mg/kg dry solid]

Exposure dose

Inhalation of air:	6.8E-06 [mg/day]	= 1.1E-07 [mg/kg/day]
Drinking water:	2.5E-05 [mg/day]	= 4.2E-07 [mg/kg/day]
Ingestion of fish:	9.0E-04 [mg/day]	= 1.5E-05 [mg/kg/day]
meat:	2.9E-10 [mg/day]	= 4.8E-12 [mg/kg/day]
milk:	3.0E-10 [mg/day]	= 5.0E-12 [mg/kg/day]
vegetation:	6.9E-08 [mg/day]	= 1.1E-09 [mg/kg/day]
Total exposure dose:	9.3E-04 [mg/day]	= 1.5E-05 [mg/kg/day]

Comparison of calculated environmental concentration of 2,2,4-trimethyl- 1,3-pentanediol diisobutyrate using several models.

Model	Air[mg/l]	Water[mg/l]	Soil[mg/kg]	Sediment[mg/kg]
MNSEM	3.4E-10	1.2E-05	7.4E-06	3.2E-03
CHEMCAN2	1.9E-09	1.3E-05	2.3E-04	3.9E-04
CHEMFRAN	1.0E-09	1.3E-05	4.5E-05	4.3E-04

Local exposure assessment (1):

1. Production volume: 450 tonnes/year
2. Emission Volume: to water 18 kg/year
   to air negligible
   waste materials none
3. Calculation of PEC_{local}
   PEC_{local} = W x 1/Q x (100-P)/100 x 1/D = 5.1E-8 mg/l
   W: 18 kg/year
   Q: 35000000 m^3/year
   P: 90 %
   D: 1000 assuming the dilution with sea water.
   The actual dilution rate must be much higher because the treated waste water is directly released to the Tokyo Bay

Local exposure assessment (2):

1. Production volume: 680 tonnes/year
2. Emission Volume: to water < 26 kg/year
   (Substance is not detected in treated waste water (5400 m^3/day) with a detection limit of 0.013 ug/ml)
   to air negligible
   waste materials none
3. Calculation of PEC_{local}
   PEC_{local} = < W x 1/Q x 1/D = 1.3E-5 mg/l
   W: < 26 kg/year
   Q: 1971000 m^3/year
   D: 1000 assuming the dilution with sea water.
   The actual dilution rate must be much higher because the treated waste water is directly released to the Tokyo Bay

2.3 Consumer Exposure

No data on consumer exposure are available.

2.4 Occupational Exposure

No data on work place monitoring have been reported.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Acute Toxicity

LD_{50} values in acute oral toxicity studies in rats were reported as > 3,200 mg/kg. LC_{50} and LD_{50} values in acute inhalation (rats) and dermal (guinea pigs) toxicity studies are 453 ppm and > 20 ml/kg, respectively.

3.1.2 Repeated Dose Toxicity

There is only one key study on repeated dose toxicity of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. This chemical was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422]. As the study was well

controlled and conducted under GLP, it was appropriate to regard this as a key study. Male and female SD rats were orally administered (gavage) at doses of 0, 30, 150 and 750 mg/kg/day. In male rats, the administration period was two weeks prior to mating, 2 weeks of mating and 2 weeks after the completion of the mating period. In females, in addition to a maximum of four weeks pre-mating and mating period, they were administered throughout the pregnant period until day 3 of post delivery.

The results in clinical observations did not reveal any effects attributable to the administration of test substance, and there was no mortality in any group. Depressions of body weight gain were observed in male rats receiving 750 mg/kg/day, and food consumption of female rats receiving 750 mg/kg/day was greater than those of control. Hematology results show that there were no essential effects of test substance. In blood clinical examination, increases in creatinine and total bilirubin were observed in rats receiving 150 and 750 mg/kg/day, and increases in total protein were observed in male rats receiving 750 mg/kg/day, suggesting that those changes were due to the effect on kidneys and liver. In organ weight analysis, increases in liver weight were observed in male rats receiving 150 and 750 mg/kg/day, moreover increases in kidneys weights were observed in male rats receiving 750 mg/kg/day. Gross findings indicate an increase in incidence of brown colored livers in male rats receiving 750 mg/kg/day. Histopathological findings indicate increases in the grade of basophilic changes of the renal tubular epithelium and degeneration of hyaline droplet in male rats receiving 150 mg/kg/day or more. Moreover, necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, decreased fatty changes and swelling of the liver cells were observed in male rats receiving 750 mg/kg/day. The NOAEL for repeated dose toxicity in rats is considered to be 30 mg/kg/day

3.1.3 Mutagenicity

Bacterial test

A reverse gene mutation assay was conducted in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guidelines 471 and 472, using the pre-incubation method. This study was well controlled and regarded as a key study.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate showed negative results in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvr*A at concentrations up to 5 mg/plate with or without a metabolic activation system (MHW, 1993).

Non-bacterial test *in vitro*

A chromosomal aberration test in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guideline 473 was conducted using cultured Chinese Hamster lung (CHL/IU) cells. Neither structural chromosomal aberrations nor polyproidy were recognized up to a maximum concentration of 0.04 mg/ml under conditions of both continuous treatment and short-term treatment with or without an exogeneous metabolic activation system (MHW, 1998).

In vivo test

No data are available on *in vivo* genotoxic effects.

3.1.4 Toxicity for Reproduction

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422] at doses of 0, 30, 150 and 750 mg/kg/day. Although this combined study was designed to investigate reproductive capability in parental generation as well as development in F_1 offspring, parameters to

evaluate developmental toxicity were limited to only body weights at day 0 and day 4 after birth, and autopsy findings at day 4.

The results observed in mating, fertility and the estrous cycle did not reveal any effects attributable to the administration of the test substance. Observation at delivery, all gestation animals delivered pups, normally and there was not a treatment-related effect throughout the lactation period. The external examination of pups revealed no effects attributable to the administration of the test substance. The body weights of pups showed favorable growths until day 4 of lactation. The necropsy of stillborn, dead pups until day 4 of lactation and newborns at day 4 of lactation did not reveal any effects attributable to the administration of the test substance. The NOAEL values for both parental and F_1 offspring in reproductive toxicity are considered to be 750 mg/kg/day.

3.2 Initial Assessment for Human Health

Neither monitoring data in the workplace nor consumer exposure has been reported. Based on the physico-chemical properties and a calculation model, the level exposed indirectly through the environment was estimated as 9.3×10^{-4} mg/man/day. The daily intake through drinking water is estimated to be 4.2×10^{-7} mg/kg/day and through fish is calculated to be 1.5×10^{-5} mg/kg/day.

The chemical showed no genotoxic effects in bacteria and chromosomal aberration tests *in vitro*.

In a combined repeated dose and reproductive/developmental toxicity screening test, increased liver and kidney weights were observed in parental animals from the middle dose level (150 mg/kg/day). In the histopathological examinations, increases in grade of basophilic changes of renal tubular epithelium and degeneration of hyaline droplet were observed from the same level. In addition, necrosis and other renal effects were also observed. From the view point of reproductive/developmental end-points, there were no effects observed related to mating, fertility and the oestrus cycle, as well as for dams during the pregnancy and lactation period and for pups after their birth. Therefore the NOEL was 30 mg/kg/day for repeated dose toxicity and 750 mg/kg/day for reproductive toxicity.

As for indirect exposure via the environment, the daily intake through drinking water is estimated to be 4.2×10^{-7} mg/kg/day and through fish, 1.5×10^{-5} mg/kg/day. The margin of safety is very large. Therefore, health risk through the environment, in general, is considered to be presumably low due to its use pattern and exposure situation.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has been tested in a limited number of aquatic species (*Selenastrum capricornutum*, *Daphnia magna* and *Oryzias latipes*), under OECD test guidelines [OECD TG 201, 202 (part I and II) and 203,]. Acute and chronic toxicity data to test organisms for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are summarized in Table 2. No other ecotoxicological data are available. Various NOEC and LC_{50} values were gained from above tests; 96h LC_{50} = 18 mg/l (acute fish); 24h EC_{50} = 300 mg/l (acute daphnia); 72h NOEC = 5.3 mg/l (algae); NOEC = 3.2 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be moderately toxic to daphnids and algae, and slightly toxic to fish. The lowest chronic toxicity data to daphnia (21d-NOEC (reproduction) for *Daphnia magna* of 3.2 mg/l) was adopted for the derivation of a PNEC. An assessment factor of 100 is applied. Thus the PNEC of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is 0.032 mg/l. Since the PEC is lower than the PNEC, the environmental risk is presumably low.

Table 2 Acute and chronic toxicity data of 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate to aquatic organisms.

Species	Endpoint[*1]	Conc. (mg/L)	Reference
Selenastrum capricornutum (algae)	Biomass: EC50 (72h) NOEC	8 mg/L 5.3 mg/L	EA, Japan. (1992)
Daphnia magna (water flea)	Mor: LC50(24h) Mor: LC50(21d) Rep: EC50(21d) NOEC(21d)	300 mg/L 12 mg/L 5.6 mg/L 3.2 mg/L	
Oryzias latipes (fish, Medaka)	Mor: LC50(24h) Mor: LC50(72h) Mor:LC50(96h)	18 mg/L 18 mg/L 18 mg/L	

Notes: [*1] Mor; mortality, Rep; reproduction.

4.2 Initial Assessment for the Environment

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a stable liquid and the production volume was ca. 1,200 tonnes/year in 1990 - 1993 in Japan. This chemical is used as an additive to plastic (plasticizer). This chemical is stable in neutral and acidic solutions, and is considered “inherently biodegradable”.

PECs have been calculated based on an emission and effluent scenario and a dilution factor. $PECs_{local}$ for aquatic compartments were 5.1×10^{-11} and 1.3×10^{-5} mg/l for Tokyo Bay.

For the environment, various NOEC and LC_{50} values were gained from test results; 96h LC_{50} = 18 mg/l (acute fish); 24h EC_{50} = 300 mg/l (acute daphnia); 72h EC_{50} = 8.0 mg/l (acute algae); NOEC = 5.3 mg/l (acute algae); 21d NOEC = 3.2 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be moderately toxic to algae and daphnids, and slightly toxic to fish. The lowest chronic toxicity data to to daphnids (21d-NOEC (reproduction) for *Daphnia magna* of 3.2 mg/l) was adopted for the derivation of a PNEC. The assessment factors of 100 were used for both acute and chronic toxicity data to determine a PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects. Thus, the PNEC of the chemical is 0.032 mg/l. The PEC is lower than the PNEC, therefore environmental risk is presumably low.

5 RECOMMENDATIONS

The chemical is currently considered of low potential risk and low priority for further work.

No further testing is needed at present considering its toxicity and exposure levels

6 REFERENCES

Aetill B.D., Terhaer C.J. & Fassett D.W. (1972) The Toxicology and fate of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, Toxicol. Appl. Pharmacol., 22, 387-399

EA, Japan (1992) "Investigation on the Ecotoxicological Effects of OECD High Production Volume Chemicals", Office of Health Studies, Environmental Health Department, Environment Agency, Japan (HPV/SIDS Test conducted by EA, Japan)

EA and MITI, Japan (1993) Unpublished Report on Exposure Estimation (HPV/SIDS Test conducted by EA and MITI, Japan)

Lyman, W.J., W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co.

MHW, Japan (1993a) Unpublished Report on Combined Repeat Dose and Reproductive/developmental Toxicity Screening Test of 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate. (HPV/SIDS Test conducted by MHW, Japan)

MHW, Japan (1993b) Unpublished Report on Mutagenicity Test of 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate. (HPV/SIDS Test conducted by MHW, Japan)

MITI, Japan: Unpublished data

MITI, Japan (1992) Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Edit CITI, Japan

MITI, Japan (1993) Unpublished Report (Test was performed in Chemicals Inspection and Testing Institute, Japan)

SIDS DOSSIER

2,2,4-Trimethyl-1, 3-pentanediol diisobutyrate

CAS No. 6846-50-0

Sponsor Country: Japan

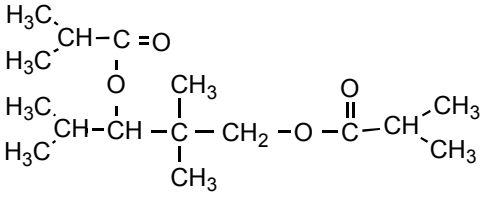
S I D S P R O F I L E

1.01 A.	**CAS No.**	6846-50-0
1.01 C.	**CHEMICAL NAME (OECD Name)**	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**STRUCTURAL FORMULA**	$C_{16}H_{30}O_4$
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	In Japan, approx 1,200 tonnes in 1990 – 1993
1.7	**USE PATTERN**	(a) main industry use Additive to plastic (Plasticizer) 97 %
1.9	**SOURCES AND LEVELS OF EXPOSURE**	1. Media of release: Water from a production site Quantities per media: Negligible small 2. Media of release: Air from a production site Quantities per media: Negligible small 3. Information on consumer exposure is not available.
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

S I D S S U M M A R Y

CAS NO: 105-05-5		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	N						N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	Y	N	N	Y	N	Y	N
	pH and pKa values	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						Y
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
3.6	Bioaccumulation	Y	Y	Y	N	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	Y	N	N	Y	N	Y	N
5.1.3	Acute Dermal	Y	N	N	Y	N	Y	N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						Y
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

1.01 SUBSTANCE INFORMATION

A.	**CAS-Number**	6846-50-0
B.	**Name** *(IUPAC name)*	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
C.	**Name** *(OECD name)*	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
D.	**CAS Descriptor**	Not applicable
E.	**EINECS-Number**	229-934-9
F.	**Molecular Formula**	$C_{16}H_{30}O_4$
G.	**Structural Formula**	
H.	**Substance Group**	Not applicable
I.	**Substance Remark**	
J.	**Molecular Weight**	286.41

1.02 OECD INFORMATION

A.	**Sponsor Country:**	Japan
B.	**Lead Organisation:**	
	Name of Lead Organisation:	Ministry of Health and Welfare (MHW) Ministry of International Trade and Industry (MITI) Environment Agency (EA)
	Contact person:	Mr. Yasuhisa Kawamura Director Second International Organization Bureau Ministry of Foreign Affairs
	Address:	2-2-1 Kasumigaseki, Chiyoda-ku Tokyo 100, Japan TEL 81-3-3581-0018 FAX 81-3-3503-3136
C.	**Name of responder**	Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element [ ]; inorganic **[ ]**; natural substance **[ ]**;
organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. Physical State

gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. Purity > 99 %

1.2 SYNONYMS Isobutyric acid, 1-isopropyl-2,2-dimethyltrimethylene

1.3 IMPURITIES 2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate

1.4 ADDITIVES None

1.5 QUANTITY

Location	Production(tonnes)	Date
Japan	1,200	1990-1993

Export (tonnes)	1993	1992	1991	1990
Thailand	145	167	197	127
Formosa	61	107	132	35
Korea	0	30	61	2

Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

None

1.7 USE PATTERN

A. General

Type of Use:	**Category:**
main industry use	Additive to plastic (Plasticizer) 97 %
MITI, Japan	

B. Uses in Consumer Products

None

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Data are not available.

1.9 SOURCES OF EXPOSURE

(a)
Source: Media of release: Water from a production site
Quantities per media: Negligible small

(b)

Source: Media of release: Air from a production site
Quantities per media: Negligible small

Reference: MITI, Japan

1.10 ADDITIONAL REMARKS

A. Options for disposal

Incineration
Reference: MITI, Japan

B. Other remarks None

2.1 MELTING POINT

Value:	< -10 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	None
Reference:	Unpublished company data

2.2 BOILING POINT

Value:	280 °C
Pressure:	at 1013 hPa
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	
Reference:	"Fire Hazard Properties of Flammable Liquids, Gases and Volatile Solids" (1991 Ed.)

2.3 DENSITY (Relative density)

No studies located

2.4 VAPOUR PRESSURE

Value:	8.8 x 10^{-2} Pa
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[X]** OECD Test Guideline 104 (Dynamic Method)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	MITI, Japan (1993)

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	> 4.11
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[**X**]** OECD Test Guideline 107
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	None
Reference:	MITI, Japan (1993)

2.6 WATER SOLUBILITY

A. Solubility

Value:	ca. 15 mg/l
Temperature:	25 °C
Description:	Miscible**[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**

Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks:
Reference: Unpublished company data

B. pH Value, pKa Value Not applicable

2.7 FLASH POINT

Value: 140 °C
Type of test: Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method: JIS K2265-1980
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks:
Reference: Unpublished company data

2.8 AUTO FLAMMABILITY

No studies located

2.9 FLAMMABILITY

No studies located

2.10 EXPLOSIVE PROPERTIES

No studies located

2.11 OXIDIZING PROPERTIES

No studies located

2.12 OXIDATION: REDUCTION POTENTIAL

No studies located

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

No studies located

B. Other data

No studies located

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type: Air **[ ]**; Water **[X]**; Soil **[ ]**; Other **[ ]**
Light source: Sun light **[X]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum:
Relative intensity:
Spectrum of substance: epsilon = 2.58 at 300 nm
Concentration of Substance:
Estimated parameter for calculation:

	Quantum yield	0.01
	Concentration	5×10^{-5} M
	Depth of water body	500 cm
	Conversion rate	6.023×10^{20}
Results:	Degradation rate	1.21×10^{-14}mol/l/s
	Half life	90.7 years

Reference W. J. Lyman, et al. (1981)

3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life: Stable at pH 4, and 7 at 25 °C
Half life time: 178 days at ph 9 at 25 °C
Method: OECD Test Guideline 111
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
Remarks: None
Reference: MITI, Japan (1993)

3.1.3 STABILITY IN SOIL

No studies located

3.2 MONITORING DATA (ENVIRONMENT)

No studies located

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

No studies located

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[X]** (Air-soil-water-sediment)

Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**;

Fugacity level IV **[ ]**;Other(calculation)**[ ]**;Other(measurement) **[ ]**

Results: Steady state mass and concentration calculated using MNSEM 147S

Air:	3.4E-10 [mg/l]
Water:	1.2E-05 [mg/l]
Soil:	7.4E-06 [mg/kg dry solid]
Sediment:	3.2E-03 [mg/kg dry solid]

Exposure dose

Inhalation of air:	6.8E-06 [mg/day]
Drinking water:	2.5E-05 [mg/day]
Ingestion of fish:	9.0E-04 [mg/day]
meat:	2.9E-10 [mg/day]
milk:	3.0E-10 [mg/day]
vegetation:	6.9E-08 [mg/day]

Total exposure dose: 9.3E-04 [mg/day]

Remarks: Input data:

Molecular weight:	286.41
Water solubility:	10.00 [mg/l]
Vapor pressure:	7.5E-04 [mmHg]
Log Pow:	4.32

MNSEM 147S is a slightly revised version of MNSEM 145I.
addition of air particle compartment to air phase
execution of calculation on a spreadsheet program

Comparison of calculated environmental concentration using several methods (Japanese environmental conditions are applied to the calculations.)

Model	Air[mg/l]	Water[mg/l]	Soil[mg/kg]	Sediment[mg/kg]
MNSEM	3.4E-10	1.2E-05	7.4E-06	3.2E-03
CHEMCAN2	1.9E-09	1.3E-05	2.3E-04	3.9E-04
CHEMFRAN	1.0E-09	1.3E-05	4.5E-05	4.3E-04

Reference: EA and MITI, Japan (1993)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No studies located

3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: 100 mg/l related to COD **[ ]**; DOC **[ ]**; Test substance **[X]**;
Medium: water **[ ];** water-sediment **[ ];** soil **[ ];** sewage treatment others [X] (Japanese standard activated sludge)
Degradation: Degree of degradation after 28 days
5, 82 and 4 % from BOD
2, 84 and 3 % from TOC analysis
4, 100 and 3 % from GC analysis

Results:	Readily biodeg. **[ ];** Inherently biodeg. **[X]**; under test condition no biodegradation observed **[ ]**, Other **[ ]**
Method:	OECD Test Guideline 301C
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
Remarks:	None
Reference:	MITI, Japan (1992)

3.6 BOD_5,COD OR RATIO BOD_5/COD

No studies located

3.7 BIOACCUMULATION

Species:	Carp
Exposure period:	6 weeks
Temperature:	25 °C
Concentration:	(1) 0.3 µg/l (2) 0.03 µg/l
BCF:	(1) 5.2 - 31 (2) 6.0 - 17
Elimination:	Yes **[ ]** No **[ ]** ? **[ ]**
Method:	OECD Test Guideline 305C
Type of test:	**[ ]** calculated; **[X]** measured static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
Remarks:	None
Reference:	MITI, Japan (1992)

3.8 ADDITIONAL REMARKS None

A. Sewage treatment

B. Other information

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]**
	open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC_{50} (24h) = 18 mg/l (95% confidence level: 8.0-40 mg/l)
	LC_{50} (48h) = 18 mg/l (95% confidence level: 11-29 mg/l)
	LC_{50} (72h) = 18 mg/l (95% confidence level: 11-29 mg/l)
	LC_{50} (96h) = 18 mg/l (95% confidence level: 11-29 mg/l)
	NOEC =
	LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 203 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate, Purity > 98%
Remarks:	A group of 10 oryzias latipes were exposed to 5 nominal concentrations (9.5-100 mg/l), DMSO control (0.5 mg/l) and laboratory control.
Reference:	EA, Japan (1992)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**;
	open-system **[**X**]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	24 hr
Results:	EC_{50} (24h) = 300 mg/l (95% confidence level:190-550 mg/l)
	EC_{50} (48h) =
	NOEC =
	LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate,
	purity = > 98 %
Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to 11 nominal concentrations (3.2-1000 mg/l) and laboratory control.
Reference:	EA, Japan (1992)

B. Other aquatic organisms

No studies located

*4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

Species:	*Selenastrum capricornutum* ATCC 22662	
End-point:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**	
Exposure period:	72 hr	
Results:	Biomass:	EC_{50} (24h) =
		EC_{50} (72h) = 8.0 mg/l
		NOEC = 5.3 mg/l ($p < 0.05$)
		LOEC =

Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 201 (1984) open-system **[**X**]**; closed-system **[ ]**
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate, purity: > 98 %
Remarks:	The EC_{50} values were calculated based on 5 nominal concentrations (5.3-55.6 mg/l) and laboratory water control.
Reference:	EA, Japan (1992)

4.4 TOXICITY TO BACTERIA

No studies located

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1. CHRONIC TOXICITY TO FISH

No studies located

(*)4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[**X**]**; flow-through **[ ]**; other **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
End-point:	Mortality **[X]**; Reproduction rate **[X]**; Other **[ ]**
Exposure period:	21 day
Results:	
Mortality:	LC_{50} (24 h) = > 32 mg/l LC_{50} (48 h) = 45 mg/l (95% confidence level: 31-110 mg/l) LC_{50} (96 h) = 20 mg/l (95% confidence level: 15-29 mg/l) LC_{50} (7 d) = 13 mg/l (95% confidence level: 9.9-16 mg/l) LC_{50} (14 d) = 12 mg/l (95% confidence level: 9.0-16 mg/l) LC_{50} (21 d) = 12 mg/l (95% confidence level: 7.9-19 mg/l) NOEC = LOEC =
Reproduction:	EC_{50} (14 d) = 5.6 mg/l (95% confidence level: 2.5-16 mg/l) EC_{50} (14 d) = 7.3 mg/l (95% confidence level: 4.9-12 mg/l) NOEC = 3.2 mg/l ($p < 0.05$) LOEC = 1.0 mg/l ($p < 0.05$)
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate, purity = > 98 %
Remarks:	40 daphnids (4 replicates; 10 organisms per replicate) were exposed to 5 nominal concentrations (0.32-32 mg/l) and laboratory water control.
Reference:	EA, Japan (1992)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No studies located

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No studies located

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No studies located

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No studies located

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No studies located

4.9 ADDITIONAL REMARKS

None

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	> 3,200 (mg/kg)
Method:	Unknown
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-trimethyl-1,3-pentanediol diisobutyrate
Remarks:	
Reference:	Aetill B.D. et al. (1972)

(b)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Mouse
Value:	> 6,400 (mg/kg)
Method:	Unknown
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-trimethyl-1,3-pentanediol diisobutyrate
Remarks:	
Reference:	Aetill B.D. et al. (1972)

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[X]**; Other **[ ]**
Species/strain:	Rat
Exposure time:	
Value:	453 ppm/6H
Method:	Unkown
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-trimethyl-1,3-pentanediol diisobutyrate
Remarks:	
Reference:	Aetill B.D. et al. (1972)

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Guinea pig
Value:	> 20 ml/kg
Method:	Unknown
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	2,2,4-trimethyl-1,3-pentanediol diisobutyrate
Comments:	
Remarks:	
Reference:	Aetill B.D. et al. (1972)

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No studies located

5.2 CORROSIVENESS/IRRITATION

No data available

5.2.1 SKIN IRRITATION/CORROSION

(a)

Species/strain:	Guinea pig
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (caused burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	2,2,4-trimethyl-1, 3-pentanediol diisobutyrate
Remarks:	5 mg/kg (Mild)
Reference:	Aetill B.D. et al. (1972)

5.2.2 EYE IRRITATION/CORROSION

No studies located

5.3 SKIN SENSITISATION

No studies located

*5.4 REPEATED DOSE TOXICITY

Species/strain:	Rat (Crj:CD(SD))
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:	Oral (gavage)
Exposure period:	Males: 44 days including 14 days before mating Females: from 14 days before mating to day 3 of lactation
Frequency of treatment:	7 days/week
Post exposure observation period:	
Dose:	0, 30, 150 or 750 mg/kg (12 animals/group)
Control group:	Yes **[X]**; No **[ ]**; No data **[ ]**; Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:	30 mg/kg/day
LOEL:	150 mg/kg/day
Results:	The results in clinical observations did not reveal any effects attributable to the administration of test substance, and there were no mortality in all groups. Depressions of body weight gain were observed in male rats receiving 750 mg/kg/day, and food consumption of female rats receiving 750 mg/kg/day was greater than those of control. As the results of hematology, there were no essential effects of test substance. In blood clinical examination, increases in creatinine and total bilirubin were observed in rats receiving 150 and 750 mg/kg/day, and increases in total protein were observed in male rats receiving 750 mg/kg/day, suggesting that those changes were due to the effect on kidneys and liver. In organ weight analysis, increases in liver weight were observed in male rats receiving 150 and 750 mg/kg/day, moreover increases in kidneys weights were observed in male rats receiving 750 mg/kg/day. As the results of gross findings, increases in incidence of brown colored livers were observed in male rats receiving 750 mg/kg/day. As the results of histopathological findings, increases in grade of

basophilic change of the renal tubular epithelium and degeneration of hyaline droplet were observed in male rats receiving 150 mg/kg/day or more. Moreover, necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, decreased fatty change and swelling of the liver cells were observed in male rats receiving 750 mg/kg/day.

Method: OECD Combined Repeat dose and Reproductive/Developmental Screening Toxicity Test (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 99.7 %
Reference: MHW, Japan (1993a)

***5.5 GENETIC TOXICITY IN VITRO**

A. BACTERIAL TEST

(a)
Type : Bacterial reverse mutation assay
System of testing:
Species/strain: *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538
E. coli uvrA
Concentration: 0, 312.5, 625, 1250, 2500 or 5000 μg/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:

Cytotoxicity conc:	With metabolic activation:	5000 μg/plate
	Without metabolic activation:	5000 μg/plate
Precipitation conc:		1250 μg/plate
Genotoxic effects:		+ ? -
	With metabolic activation:	**[ ] [ ] [X]**
	Without metabolic activation:	**[ ] [ ] [X]**

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Teat substance: Purity: 99.7 %
Remarks: Procedure: Plate method
Plates/test: 3
Activation system: Liver S-9 fraction from Phenobarbital and 5,6-Benzoflavone pretreated male SD rats with NADPH-generating system
Media:Histidine selective
No. replicates: 2
Reference: MHW, Japan (1993b)

B. NON-BACTERIAL IN VITRO TEST

Type : Cytogenetics Assay
System of testing: Species/strain: Chinese hamster CHL cells
Concentration:
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:

Cytotoxicity conc:	With metabolic activation:	0.018 mg/ml
	Without metabolic activation:	0.04 mg/ml
Precipitation conc:		
Genotoxic effects:		+ ? -
	With metabolic activation:	**[ ] [ ] [X]**
	Without metabolic activation:	**[ ] [ ] [X]**

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals

GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity 99.7 %
Remarks: Plates/test: 2
Activation system: S-9 fraction from the liver of Phenobarbital and 5,6-Benzoflavone induced male SD derived rats with NADPH-generating system
No. replicates: 1
Reference: MHW, Japan (1993b)

5.6 GENETIC TOXICITY IN VIVO

No studies located

5.7 CARCINOGENICITY

No studies located

*5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One generation study **[ ]**; Two generation study **[ ]**; Other **[X]**
Species/strain: Rat (slc:SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Males: 44 days including 14 days before mating
Females: from 14 days before mating to day 3 of lactation.
Frequency of treatment: 7 days/week
Postexposure observation period:
Premating exposure period: male: 14 days, female: 14 days
Duration of the test;
Doses: 0, 30, 150, or 750 mg/kg (12 animals/sex/group)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**;
Historical **[ ]**
NOEL Parental: 750 mg/kg/day
NOEL F1 Offspring: 750 mg/kg/day
NOEL F2 Offspring: N/A
Results: The results observed in mating, fertility and estrous cycle did not reveal any effects attributable to the administration of test substance. Observation at delivery, all gestation animals delivered of pups, normally and there were not a treatment-related effect throughout the lactation period. The external examination of pups revealed no effects attributable to the administration of test substance. The body weights of pups showed the favorably growths until day 4 of lactation. The necropsy of stillborn, dead pups until day 4 of lactation and newborns at day 4 of lactation did not reveal any effects attributable to the administration of test substance.
Method: Combined Repeated Dose and Reproductive/Developmental toxicity Screening Test
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity 99.7 %
Remarks: None
Reference: MHW, Japan (1993a)

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

No studies located

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No studies located

B. Toxicodynamics, toxicokinetics

No studies located

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

None

Aetill B.D., Terhaer C.J. & Fassett D.W. (1972) The Toxicology and fate of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, Toxicol. Appl. Pharmacol., 22, 387-399

EA, Japan (1992) "Investigation on the Ecotoxicological Effects of OECD High Production Volume Chemicals", Office of Health Studies, Environmental Health Department, Environment Agency, Japan (HPV/SIDS Test conducted by EA, Japan)

EA and MITI, Japan (1993) Unpublished Report on Exposure Estimation (HPV/SIDS Test conducted by EA and MITI, Japan)

Lyman, W.J., W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co.

MHW, Japan (1993a) Unpublished Report on Combined Repeat Dose and Reproductive/ developmental Toxicity Screening Test of 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate. (HPV/SIDS Test conducted by MHW, Japan)

MHW, Japan (1993b) Unpublished Report on Mutagenicity Test of 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate. (HPV/SIDS Test conducted by MHW, Japan)

MITI, Japan: Unpublished data

MITI, Japan (1992) Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Edit CITI, Japan

MITI, Japan (1993) Unpublished Report (Test was performed in Chemicals Inspection and Testing Institute, Japan)