FOREWORD INTRODUCTION

1,4-BUTANEDIOL

CAS N°:110-63-4

SIDS Initial Assessment Report
for
10th SIAM
(Tokyo, March 15-17, 2000)

Chemical Name: 1,4-Butanediol
CAS No: 110-63-4
Sponsor Country: Japan

National SIDS Contact Point
in Sponsor Country: Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs, Japan

HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient
Stability in water, Biodegradation
Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity
Gene mutation, Chromosomal aberration test in vitro

First Discussion was conducted at SIAM 9.
Deadline for circulation: November 30, 1999
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(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	110-63-4
CHEMICAL NAME	1,4-Butanediol
STRUCTURAL FORMULA	$HO\text{-}CH_2CH_2CH_2CH_2\text{-}OH$

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is a candidate for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

Human Health

Acute lethal toxicity of 1,4-butanediol is low via all administration routes. Major toxicity by oral administration is respiratory failure and catalepsy. This chemical is a slight irritant to the skin, eyes and respiratory tract, but not a skin sensitizer. As 1,4-butanediol is rapidly absorbed and metabolized to γ-hydroxybutyric acid in animals and humans, neurotoxic effect of 1,4-butanediol such as depression of central nervous system is considered to be caused by the metabolite, γ-hydroxybutyric acid. 1,4-Butanediol seems to show a competitive inhibition of alcohol dehydrogenase and increase the toxic effect of alcohol.

In an OECD combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422), rats were administered by gavage at doses of 200, 400 and 800 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. Neurobehavioral toxicity (i.e. hyperactivity and coma after hypoactivity and recumbency) and pathological changes (diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder) were observed. The transient hyperactivity only just after administration was observed at the lowest dose of 200 mg/kg/day. This neurotoxicity in dams was also observed in developmental toxicity study of mice at doses of 300 and 600 mg/kg/day by gavage during gestational days 6-15 but not at 100 mg/kg/day. This study was conducted by NTP test guideline under GLP. Therefore NOAEL of 100 mg/kg/day for oral repeated toxicity is sufficiently reliable.

In a 2 week inhalation rat study at 1.1 g/m^3 (6 hours/day, 5 days/week), no changes including neurotoxicity were observed. Therefore, 1.1 g/m^3 was considered to be inhalation NOAEL. Repeated intraperitoneal administration induced narcotic effect at more than 500 mg/kg/day, but NOAEL was not established.

From repeated dose studies, it is evident that critical effect is neurotoxicity. However, the nature of the data does not allow for the identification of the dose-response and NOAEL

for this effect.

As for reproductive toxicity, a reduction in fetal body weight of rats was observed in the above OECD combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422) but this effect was considered to be secondary to maternal toxicity. NOAEL for reproductive toxicity is the highest dose of 800 mg/kg/day. In the developmental toxicity study of mice at 100, 300 and 600 mg/kg/day described above, the only definitive expression of developmental toxicity was a reduction in average fetal body weight at doses of 300 and 600 mg/kg/day (92% and 83% of control weight, respectively). However, this effect against foetal development was considered to be secondary to maternal toxicity. No teratogenicity was observed at any doses. Thus, 600 mg/kg/day is the developmental NOAEL. Genotoxicity of this chemical may be negative because of neither bacterial mutation in *S. Typhimurium* TA100, TA98, TA1535, TA1537, and *E.coli* WP2 *uvr*A with and without metabolic activation (OECD TG 471 and 472), nor chromosomal aberration *in vitro* in CHL/IU cells with or without metabolic activation system OECD TG (473).

Environment

1,4-Butanediol is a liquid at 20 °C, and this chemical is classified as a readily biodegradable chemical (OECD 301C: 100 % after 14-day). Bioconcentration factor may be low judging from a low P_{ow} value (0.50 at 25 °C).

The lowest acute and chronic toxicity data were 14d LC50 (>100 mg/l) of fish (Medaka; *O. latipes*) and 21d NOEC (> 85 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, because chronic toxicity data for fish were not available. Thus, PNEC of this chemical is >0.85 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 85 mg/l.

Exposure

The production volume of this chemical was 29,717 tones in 1993 in Japan. This chemical is used as an intermediate for resins and/or solvents in closed system, and not included in consumer products of Sponsor county. The potential environmental distribution of this chemical obtained from a generic fugacity model (Mackey level III) shows that this chemical will be distributed mostly in water (99.6 %) and partly in sediment (0.4%) when it is discharged into water. The route of occupational exposure is inhalation and skin with a limited numbers of workers. As for consumer use, this chemical is used as an ingredient in deodorants in European countries, and marketed as dietary supplement in US.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

Human health

Further exposure information should be collected in each member country.

FULL SIDS SUMMARY

CAS NO: 110-63-4		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			20 °C
2.2	Boiling Point			235 °C
2.3	Density			
2.4	Vapour Pressure		OECD TG104	1.9 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	0.50
2.6 A.	Water Solubility		OECD TG 105	100 g/L at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4, 7 and 9
3.2	Monitoring Data			Surface water : ND Sediment : ND
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to water In Air 0.0 % In Water 99.6 % In Sediment 0.4 % In Soil 0.0 %
			(local exposure)	1.1 x 10^{-3} mg/L (Japan)
3.5	Biodegradation		OECD TG 301C	Readily biodegradable 100% in 14 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50}(48hr): > 100 mg/l LC_{50}(72hr): > 100 mg/l LC_{50}(96hr): > 100 mg/l LC_{50}(14d): > 100 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50}(48hr): > 1000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50}(72hr): > 1000 mg/l NOEC: > 1000 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(21d, Repro): > 85 mg/l NOEC: > 85 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None

CAS NO: 110-63-4		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 1.8 g/kg
5.1.2	Acute Inhalation Toxicity	Rat	OECD TG 403	LC_{50} > 5.1 g/m^3/4h
5.1.3	Acute Dermal Toxicity	Rat	Other (unknown)	LD_{50} > 5.0 g/kg
5.2.1	Skin irritation/corrosion	Rabbit	Other (unknown)	slight irritating
5.2.2	Eye irritation/corrosion	Rabbit	Other (unknown)	slight irritating
5.3	Skin sensitisation	Guinea pig	Other (unknown)	not sensitising
5.4	Repeated Dose Toxicity	Mouse	RTI 360/NTP-90-CTER-133	NOAEL = 100 mg/kg/day
		Rat	Other (inhalation)	NOAEL = 1.1 g/m^3/6 h, 5 day/wk
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli*	Japanese TG and OECD TG 471 and 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo	Drosophila melanogaster	Other (unknown)	- (Questionable data)
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL = 800 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity	Mouse	RTI 360/NTP-90-CTER-133	NOAEL = 600 mg/kg/day
5.11	Experience with Human Exposure			Neurotoxic

SIDS INITIAL ASSESSMENT REPORT

1,4-Butanediol (CAS No. 110-63–4)

1. IDENTITY

- OECD Name: 1,4-Butandiol
- Synonym: 1,4-Butylene glycol; 1,4-Dihydroxybutane; Tetramethylene glycol; Butanediol; Butane-1,4-diol; 1,4-Tetramethylene glycol; Butylene glycol; Tetramethylene-1,4-diol
- CAS Number: 110-63-4
- Empirical Formula: $C_4H_{10}O_2$
- Structural Formula: $HO\text{-}CH_2CH_2CH_2CH_2\text{-}OH$
- Degree of Purity: 98.0 %
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 20 °C
  - Vapour pressure: 1.9 Pa at 25 °C
  - Water solubility: > 100 g/L
  - Log Pow: 0.50

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of 1,4-butandiol in Japan is 29,717 tonnes/year in 1995.

2.2 Use pattern

All of 1,4-butandiol produced in Japan is used as intermediate for resin, and no consumer use is reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

1,4-Butandiol is readily biodegradable (OECD 301C: 100 % after 14 d). Direct photodegradation is not expected because 1,4-butandiol has not absorption band in UV and VIS region.

1,4-Butandiol is low bioaccumulative based on Log Pow (0.5 at 25 °C).

The potential environmental distribution of 1,4-butandiol obtained from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if 1,4-butandiol is released into water, it is unlikely to be distributed into other compartment. If 1,4-butandiol is released into air or soil, it is likely to be distributed in water and soil.

Table 1 Environmental distribution of 1,4-butandiol
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.4 %	0.0 %	0.0 %
Water	47.7 %	99.6 %	41.4 %
Soil	51.6 %	0.0 %	58.4 %
Sediment	0.2 %	0.4 %	0.2 %

As this chemical is used in closed system as an intermediate and is not included in consumer products, its release to the environment may occur only from the production site.

3.1.2 Predicted Environmental Concentration

As 1,4-butandiol is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of 1,4-butandiol from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 4,000 kg/year (measured) of 1,4-butandiol are treated in its own wastewater treatment plant with 95 % of removal rate and released with 7.2×10^8 L/year of effluent into river which has flow rate of 1.82×10^{11}L/year at dry season. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 1.1×10^{-3} mg/L as a worst case scenario, employing the following calculation model and dilution factor of 253.

$$\frac{\text{Amount of release } (4 \times 10^9 \text{ mg/y}) \times (1 - \text{Removal rate } (95\%))}{\text{Volume of effluent } (7.2 \times 10^8 \text{ L/y}) \times \text{Dilution Factor } (253)}$$

3.2 Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of 1,4-butanediol to aquatic organisms are summarized in Table 2. These toxicity data were mostly obtained by GLP laboratories, and the data were calculated based on the measured concentrations, which were kept in the levels from 85 to 102 % of the nominal concentrations throughout the tests.

As the lowest acute and chronic toxicity data, 14 d LC50 of fish (*Oryzias latipes*) and 21 d NOEC (reproduction) of *Daphnia magna* were adopted, respectively (Table 2).

Toxicity of this chemical to aquatic organisms seems to be low, because all toxicity data obtained were higher than 85 mg/l (100 mg/l as nominal concentration) or 1000 mg/l which are maximum

concentration exposed. No fish died, and no toxic symptoms were observed in fish exposed to 92.5 mg/l (measured concentration of the nominal 100 mg/l) of this chemical throughout 14d test period. Also, any reproduction impairment was not observed in *D. magna* exposed to 85 mg/l (measured concentration of the nominal 100 mg/l).)

An assessment factor of 100 was chosen and applied to chronic toxicity data to determine PNEC, because chronic toxicity data for fish were not available. Thus, PNEC of this chemical is >0.85 mg/l.

Table 2. Acute and chronic toxicity data of 1,4-butanediol to aquatic organisms at different trophic levels.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72h EC50	> 1000	a, 1)
	Bms 72h NOEC	> 1000	c, 1)
Daphnia magna (water flea)	Imm 48h EC50	> 1000	a, 1)
	Rep 21d EC50	> 85	c, 1)
	Rep 21d NOEC	> 85	c, 1), C
Oryzias latipes (fish, Medaka)	Mor 48h LC50	> 100	a, 1)
	Mor 48h LC50	> 100	a, 1)
	Mor 96h LC50	> 100	a, 1)
	Mor 14d LC50	> 100	a, 1), A

Notes: Bms; growth measured by biomass change, Imm; immobilization, Mor; mortality, Rep; reproduction. 1); reference number. A, C; the lowest values of the acute (a) or chronic (c) toxicity data among algae, cladocera (water flea) and fishes.

Reference; 1) Environment Agency of Japan (1996).

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

1,4-Butanediol is readily biodegradable (OECD 301C: 100% after 14-d) and has a low log P_{ow}, (0.5 at 25°C). The lowest acute and chronic toxicity values were >100 mg/l (14 d LC50 of fish, *O. latipes*) and >85 mg/l (21 d NOEC of *D. magna*), respectively. Thus, this chemical seems not to be hazardous to the aquatic environment

PNEC of this chemical is > 0.85 mg/l based on 21d NOEC of *Daphnia* and the assessment factor 100. PEC from Japanese local exposure scenario is 1.1×10^{-3} mg/l. Thus, PEC_{local} / PNEC = $1.1 \times 10^{-3}/(>0.85) = < 0.0013 < 1$

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

1,4-Butanediol is produced in closed systems and used for resin synthesis and as a solvent. The occupational exposures are expected through inhalation and dermal route. As the atmospheric concentration in plant was not measured, the maximum exposure levels are estimated according to a scenario and working schedules as follows. Dermal exposure is also calculated, based on EASE model. The duration of dermal exposure is assumed to be 5 minutes. The maximum concentration is calculated as 184 mg/m^3 at sampling and lorry filling. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hour) is assigned to implement all daily operation without protection, the highest daily intake (combined EHE) is calculated as 3.2 mg/kg/day as the worst case. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hour/day	Maximum Concentration mg/m^3	Maximum EHE mg/kg/day	Combined EHE mg/kg/day
Sampling	1	0.5	0.5	184	1.6	
Dermal			0.08	1 *	0.00625	
Lorry Filling	1	0.5	0.5	184	1.6	
Dermal			0.08	1 *	0.00625	3.2

* dermal exposure; mg/cm^2/day
EHE: Estimated Human Exposure

4.1.2 Consumer exposure

1,4-Butanediol is used as a raw material for resins, plastics and other industrial chemicals in Sponsor country. However, in European countries, this chemical is used as an ingredient in deodorants. In US, this chemical is marketed as dietary supplement.

4.1.3 Indirect exposure via the environment

Although 1,4-butanediol is readily biodegradable and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 1.1 x 10^{-3} mg/L. The daily intake through drinking water is calculated as 3.67 x 10^{-5} mg/kg/day (2 l/day, 60 kg b.w.).

Using bioconcentration factor of 10 estimated from log Pow, the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = (1.10 \times 10^{-3} \text{ mg/l}) \times 10 = 1.10 \times 10^{-5} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 1.65 x 10^{-5} mg/kg/day.

4.2 Effects on Human Health

a) Motion of action of the chemical, toxicokinetics and metabolism

Single dose study on 1,4-butanediol using guinea pigs and rats suggested an absence of any marked cumulative properties (Knyshova: 1968). Poldrugo and Snead (1984) indicated that this chemical appeared to have two types of pharmacologic actions, one attributable to its conversion to γ-hydroxybutyric acid and the other an inherent property of the diol itself. It is generally accepted that γ-hydroxybutyric acid crosses the blood-brain barrier and shows neuropharmacologic responses same as 1,4-butanediol. Therefore, neurotoxic effect of 1,4-butanediol is considered to be caused by the metabolite, γ-hydroxybutyric acid. Recently, a metabolism and disposition study conducted in F344/N rats by the NTP confirmed the rapid and extensive conversion of 1-(^{14}C)-1,4-butanediol to $^{14}CO_2$ (NTP working group: 1996). Based on these information, it is considered that 1,4-butanediol is rapidly absorbed and metabolized to γ-hydroxybutyric acid in animals as well as humans.

Poldrugo and Snead (1986) showed the importance of the enzymatic reaction responsible for the conversion of 1,4-butanediol to γ-hydroxybutyric acid in brain and liver. The enzyme was considered to be alcohol dehydrogenase. 1,4-Butanediol potentiated some of the behavioural effects of ethanol perhaps by a mechanism of action similar to that of other alcohols (Poldrugo and Snead: 1984, Poldrugo *et al.*: 1985). On the other hand, the simultaneous administration of ethanol, which likely block conversion of 1,4-butanediol to γ-hydroxybutyric acid, increased in a concentration of 1,4-butanediol in tissues of rats, resulting in increase in the mortality rate and tissue damage induced by 1,4-butanediol (Poldrugo *et al.*: 1985).

b) Acute toxicity

The LD_{50} values for 1,4-butanediol via various administration routes are shown in the following Table. As the most common signs of toxicity by oral administration, lateral posture, irregular decreased respiration and catalepsy were observed, and gross pathological findings in animals that died showed congestion of internal organs. In inhalation study, there were some slight respiratory clinical signs such as accelerated respiration, shallow respiration etc. and these changes disappeared 1 day after exposure although no mortality was observed in rats at 5.1 g/m^3 (BASF: 1991). No mortality in rats was reported in dermal study at 5,000 mg/kg b.w. (Jedrychowski *et al.*: 1990a). The histopathological changes were limited to the skin and liver.

Routes	Strain	Type	Values	Reference
Oral	Rats	LD_{50}	1,830 mg/kg b.w.	Jedrychowski *et al.*: 1990a
	Rats	LD_{50}	1,525 mg/kg b.w.	Knyshova: 1968
	Mice	LD_{50}	2,060 mg/kg b.w.	Knyshova: 1968
	Rabbits	LD_{50}	2,531 mg/kg b.w.	Knyshova: 1968
	Guinea pigs	LD_{50}	1,200 mg/kg b.w.	Knyshova: 1968
Intraperitoneal	Rats*	LD_{50}	1,070 mg/kg b.w.	Taberner and Pearce: 1974
	Rats	LD_{50}	1,330 mg/kg b.w.	Zabik *et al.*: 1974
	Mice	LD_{50}	1,660 mg/kg b.w.	Holman *et al.*: 1979

Subcutaneous	Mice	LD_{50}	2,000 mg/kg b.w.	Dominguez-Gil and Cadorniga: 1971
Intravenous	Mice	LD_{50}	1,000 mg/kg b.w.	Dominguez-Gil and Cadorniga: 1971

* LD_0 and LD_{100} were approx. 900 and 1800 mg/kg, respectively. At 900 mg/kg, there was a characteristic hypnotic state, with loss of the righting reflex and maintained muscle tone, after a latency of about 20 min after injection. Increasing the dose produced an increase in the depth of hypnosis together with a marked bradycardia, analgesia and laboured respiration. Death appeared to be due to respiratory failure.

c) Irritation

Skin irritation
The gauze patches with undiluted 1,4-butanediol were applied to the intact and abraded skin of rabbits with occlusive dressing for 24 hours. After 1, 24, 48 and 72 hours, no reaction was observed on the intact and abraded skin. These rabbits were used to assess short-term dermal irritation. The internal areas of the right ears of rabbits were painted with either 100 % or 50 % of 1,4-butanediol in water for 10 consecutive days. After 10 days of exposure period, a minimal reddening was observed in 100 % treated group. (Jedrychowski *et al.*: 1990a)

In another study, repeated application to both intact and abraded skin resulted in no appreciable irritation and no evidence of absorption of acutely toxic amounts (Knyshova: 1968).

In human, skin test on 200 persons showed no irritation although there was no more data (GAF: 1967).

Eye irritation
1,4-Butanediol was administered to the right conjunctival sac of rabbits as a single dose of 0.1 mL. Slight reddening of the conjunctives and small amounts of discharge were observed in all four rabbits 1 hour after ocular application. The changes diminished after 24 and 48 hours and no abnormalities were observed thereafter. (Jedrychowski *et al.*: 1990a)

In another study, there was also very slight conjunctival irritation but no corneal injury (Rowe and Wolf: 1982). Knyshova (1968) reported that ineffective concentration of 1,4-butanediol with respect of ocular mucosa was determined 500 mg/L.

Respiratory irritation
In acute inhalation study, some slight respiratory clinical signs (accelerated respiration, shallow respiration etc.) were observed during and just after exposure at 5.1 g/m^3 (as a liquid aerosol) (BASF: 1991). In another study, male rats were exposed nose-only for 4 hours to 4.6, 9.4, or 15.0 g/m^3 (Kinney *et al.*: 1991). After the exposure, rats at 4.6 and 9.4 g/m^3 were lethargic with laboured breathing. At 15.0 g/m^3, red discharge was observed in the perineal area. A few rats at 9.4 and 15.0 g/m^3 had noisy respiration and dry red nasal discharge lasting 1-9 days post-exposure.

This chemical is not listed on EC classification.

Based on these data, 1,4-butanediol is considered an irritant to the skin, eyes and respiratory tract. This effect is likely slight, especially very slight to the skin.

d) Sensitisation

Maximization test was performed in guinea pigs. In induction procedure, 1,4-butanediol was applied at a concentration of 10 % (intradermal injections) and 30 % (topical application). The challenge procedure was done with 10 % and 30 % 1,4-butanediol. As a result, no allergic contact dermatitis was induced. (Jedrychowski et al.: 1990a)

In human, skin patch test on 200 persons indicated no sensitization (GAF: 1967).

Therefore, 1,4-butanediol is not considered a skin sensitizer.

e) Repeated toxicity

As an oral toxicity study, 1,4-butanediol was administered to Wistar Imp:DAK rats by gavage at doses of 5, 50 or 500 mg/kg/day for 28 consecutive days. A statistically significant increase in activities of sorbitol dehydrogenase and alanine aminotransferase was observed at 500 mg/kg/day in males. Proliferation of bile ducts and periportal infiltrations with fibroblasts and mononuclear cells were found in liver of treated animals but not statistically significant. However this became significant at 500 mg/kg/day only in the case where both sexes were jointly taken for comparison. The author considered that the proliferation of bile ducts and periportal mononuclear dell infiltrations were indices of chronic toxic inflammation of the liver. (Jedrychowski *et al*.: 1990b)

However, there was no description on neurotoxic effect, being observed in the other oral studies and the hepatic inflammation was not observed even at higher doses in other oral studies. Furthermore, only five in eight animals of each group were histopathologically examined and the severity of bile duct proliferation was not given. Therefore, reliability of this study is considered to be questionable.

Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. Administration was conducted at doses of 200, 400 or 800 mg/kg/day by gavage for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1999)

Acute and transient toxic signs in central nervous system were observed in both sexes, and severity of the sign increased with dosage levels. The transient hyperactivity only just after administration was observed at 200 mg/kg/day. At 400 mg/kg, activities were rather suppressed than increased although hyperactivity was also observed after a few doses. At 800 mg/kg, toxic signs observed were more severe and some animals were even comatose after showing hypoactivity and recumbency. By 5 hours after dosing, these signs disappeared and animals recovered to normal. Body weight gains were suppressed at 400 and 800 mg/kg during the early period of administration. The weight gains were not further suppressed thereafter, the difference in body weight produced during the early period of administration remained until termination of the study. Food consumption also decreased accordingly. In the histopathological examination, diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder were observed in the 400 and 800 mg/kg groups. Authors considered that hyperactivity at 200 mg/kg was not adverse effect.

However, Japanese assessment committee concluded that the hyperactivity at 200 mg/kg was adverse effect and NOAEL was not published in this study.

As a developmental toxicity study, female pregnant Swiss (CD-1) mice were given 1,4-butanediol (0, 100, 300 or 600 mg/kg/day) by gavage for 10days (Price *et al.*: 1993). This study was conducted by NTP test guideline under GLP.

Animals at the mid and high doses exhibited symptoms of central nervous system intoxication (hypoactivity, immobility, loss of righting reflex and/or prone posture) during the first 4 hr following daily administration. Any neurotoxic effect was not observed at the low dose. Thus, 100 mg/kg/day was NOAEL.

In an inhalation study, male rats were exposed to 1,4-butanediol at concentrations of 1.5 - 2 g/m^3, 2 hours/day, daily for 4 months. Inactive and sleepy condition was induced after 3- or 4-week exposure and these changes appeared at 10 to 20 minutes after the exposure. Histopathological examination revealed a lot of pulmonary emphysema and the mild lung edema. In a few animals, there were the inflammatory changes of single alveolar cell and weak hyperplasia of alveolar septum with proliferation of lymphocytes and histiocytes. These histopathological changes were considered to be due to the irritation of 1,4-butanediol. There were no-treatment related pathological changes in any other organs. LOAEL was 1.5 g/m^3 (85 mg/kg/day). (Stasenkova: 1965)

In further study by the same group, male rats were exposed to 1,4-butanediol at concentrations of 0.3 – 0.5 g/m^3, 2 hours/day, 6 days/week for 4 months. It was reported that body weight, function of nervous system (neuromuscular response) and hemogenesis as well as liver and kidney function were not changed. 0.5 g/m^3 (equivalent to 23 mg/kg/day) was considered to be NOAEL. (Stasenkova: 1965)

As a recent inhalation study, male Crl: CD rats received nose-only exposure to aerosol of 1,4-butanediol at 0.20, 1.1, or 5.2 g/m^3, 6 hours/day, 5 days/week for 2 weeks. Daily intake was calculated as 24, 134, or 634 mg/kg/day, respectively. Rats were given pathology, urinalysis, and clinical chemical examinations after the last exposure and after a 2-week recovery period. Mean body weights for rats exposed to 5.2 g/m^3 were significantly lower than the controls from the third exposure day to 4 days post-exposure. There was a significant decrease in heart weights after ten exposures at 5.2 g/m^3. In hematological examination, there was a significant increase in erythrocyte counts and hematocrits, and a significant decrease in serum cholesterol concentrations when sacrificed immediately after the tenth exposure to 5.2 g/m^3. Pathological examination showed slight atrophy of lymphoid cells in the thymus in 3/5 rats exposed to 5.2 g/m^3. These changes at 5.2 g/m^3 returned to normal during the recovery period. No adverse effects were observed in rats exposed to either 0.20 or 1.1 g/m^3. NOAEL was considered to be 1.1 g/m^3 (134 mg/kg/day) under the conditions of this test. (Kinney et al.: 1991)

Male Sprague-Dawley rats were treated intraperitonealy at 500 and 1,000 mg/kg/day daily for 10 or 14 days. In 4-day treatment study (Zabik *et al.*: 1974), narcotic effect was observed but reduced in progress of the study. However, the doses at which this change appeared were not mentioned. In 14-day treatment study (Zabik *et al.*: 1973), body weight gain was slightly depressed, and plasma and liver free fatty acids and triglycerides were slightly changed at 1,000 mg/kg/day. NOAEL could not be published.

By oral administration, the most reliable NOAEL is considered to be 100 mg/kg/day, based on the disappearance of neurotoxicity in mouse developmental toxicity study. This conclusion is confirmed by the result of an OECD combined rat study (TG 422). In an inhalation study, the appropriate NOAEL is considered to 1.1 g/m^3, based on no adverse effects including neurotoxicity. Via an intraperitoneal route, narcotic effect was induced at more than 500 mg/kg/day, but NOAEL was not established.

f) Reproductive/developmental toxicity

Reproductive toxicity

Oral toxicity study on 1,4-butanediol was performed in SD (Crj: CD) rats by an OECD combined repeated dose and reproductive/developmental toxicity screening test (TG 422). Administration was conducted by gavage at doses of 200, 400 or 800 mg/kg /day from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: in preparation)

The parental animals exhibited no alteration in reproductive parameters including the copulation index, fertility index, gestation length, numbers of corpora lutea or implantation, implantation index, gestation index, delivery index, and behavior at delivery and lactation. Although neither the pup viability nor the incidence of morphological abnormalities was changed by administration of the compound, pup body weight was slightly but significantly decreased in the 800 mg/kg group. This change was considered to be secondary to maternal toxicity (reduced food consumption and body weight gain). Therefore, NOAEL for reproductive toxicity was 800 mg/kg/day.

Developmental toxicity

Timed-pregnant Swiss (CD-1) mice (28-32/group) were given 1,4-butanediol (0, 100, 300 or 600 mg/kg/day) by gavage during major organogenesis (gestational days 6-15). Maternal body weight, clinical signs and food/water intake were monitored at regular intervals throughout gestation. On days 17, implant survival, fetal weight and, sex and morphological development (external, visceral and skeletal) were examined. (Price *et al.*: 1993)

There were no maternal deaths in this study. No maternal or developmental effects were observed at the low dose. Dams (60-100 %/group/day) at the mid and high doses exhibited symptoms of central nervous system intoxication (hypoactivity, immobility, loss of righting reflex and/or prone posture) during the first 4 hr following daily administration. Maternal effects at the mid and high doses also included reduced food intake (treatment and post treatment periods), reduced body weight, and reduced weight gain (treatment period, gestation period and corrected weight gain). The only definitive expression of developmental toxicity was a reduction in average fetal body weight at the middle and high doses (92% and 83% of control weight, respectively). However, this effect against fetus is considered to be secondary to maternal toxicity. No teratogenicity was observed at any doses. Thus, 600 mg/kg/day was the developmental NOAEL.

g) Genetic toxicity

Bacterial test

Gene reverse mutation was negative in *S. Typhimurium* TA100, TA98, TA1535, TA1537 and *E.coli* WP2 *uvr*A with and without metabolic activation by OECD TG 471 and 472 (MHW, Japan: 1997).

Non-bacterial test *in vitro*

Clastogenicity or polyploidy in CHL/IU cells by chromosomal aberration test was not induced in the absence or presence of an exogenous metabolic activation system by OECD TG 473 (MHW, Japan: 1997).

As another chromosomal aberration test, metaphase chromosome analysis was performed in V79 Chinese hamster lung cell (Hüls AG: 1993a). In this test, 1,4-butanediol was not clastogenic with and without metabolic activation, either.

In gene mutation assay using CHO cells, 1,4-butanediol did not induce any reproducible statistically or biologically significant increase in the mutant frequency of the HPRT

(hypoxanthine-guanine phosphoribosyl transferase) locus with and without metabolic activation (Hüls AG: 1993b).

in vivo test
Genotoxicity test in vivo using Drosophila melanogaster showed the negative results but Lee *et al.* (1983) commented that its result was questionable because of inadequate sample size.

Therefore, 1,4-butanediol is considered not to be genotoxic.

h) Any other human health related information that is available

1: Specific toxicities

Neurotoxicity
The six months long-term experiment was carried out after preliminary tests for their ability to form conditioned reflexes in order to reveal the background of their physiological and biochemical reactions. Male rats (6 animals/group) received 0.25, 3.0, 30 mg/kg of 1,4-butanediol (no information on exposure route). (Knyshova: 1968)

The animals at 30 mg/kg lagged with respect to the appearance and fixation of the reflex and had a longer latent period before responding to the bell. At the end of exposure, there was a significant decrease in SH groups in the gray matter of the brain. In morphological examination, there were reduced content of Nissl bodies and the growth of glial elements in the cerebral tissue, fatty dystrophy and areas of sclerotic growth in liver and patchy hyperemia in the other organs at 30 mg/kg. At 3.0 mg/kg, morphological changes observed were regarded as incipient or liminal.

This report is not reliable since details of experimentation and documentation are not given and this is too old report. In addition, the endpoints tested do not give any prove of neurotoxicity. There is no evidence of irreversible structural changes, less Nissl bodies is no indication of neurotoxicity, growth of glial elements does not give any relevant information, and change of SH-groups is not a known parameter for neurotoxic activity.

In another study, rats were given 0.5 % of 1,4-butanediol in drinking water (approx. 508 mg/kg/day) daily for 10 days. No clinical and pathological changes were observed in central and peripheral nervous systems.

Effect on body temperature
1,4-Butanediol (500 mg/kg) was administered intraperitoneally to Wistar albino rats (Taberner and Pearce: 1974). A fall in body temperature of 1.0 - 2.0 °C occurred about 0.5 to 4 hours after administration of 1,4-butanediol, when the loss of righting reflex was induced. This fall can be considered to be the results of the depressant action of the drugs, although a direct central hypothermic action cannot be ruled out.

Interaction
There were some data on interaction of 1,4-butanediol with ethanol. The simultaneous administration of ethanol increased the mortality rate and tissue damage induced by in rats. Increase in a concentration of 1,4-butanediol in tissue was observed. (Poldrugo *et al.*: 1985) The enzymatic reaction responsible for the conversion of 1,4-butanediol to γ-hydroxybutyric acid and the interaction of ethanol with this conversion in brain and liver were examined. The enzyme responsible for this reaction in liver appeared to be alcohol dehydrogenase. In both tissues, there was a competitive

inhibition by ethanol of the conversion of 1,4-butanediol to γ-hydroxybutyric acid with an apparent Ki of 6.5 x 10^{-3} M in brain and 2.7 x 10^{-3} M in liver. (Poldrugo and Snead: 1986)

In acute toxicity study, interaction between 1,4-butanediol and pyrazole (an inhibitor of liver dehydrogenase) was examined. Administration with only 1,4-butanediol (17.80 mmol/kg, i.p.) induced behavioral changes and death (6/6 animals). Pretreatment with pyrazole (2.9 mmol/kg, i.p.) prevented these effects. (Taberner and Pearce: 1974)

Based on these data, 1,4-butanediol was considered to competitively inhibit alcohol dehydrogenase, which catalysed the conversion of 1,4-butanediol to γ-hydroxybutyric acid.

2: Experience with human exposure

15 or 30 g of 1,4-butanediol (0.21 or 0.43 g/kg b.w.) was rectally administered to 7 patients. After 10 to 20 minutes, the patients became coma after deep unconsciousness, miosis and complete areflexia and this condition continued for 1 to 16 hr. Two of them died with in 72 hours after the administration, but other five patients recovered naturally or after treatment with analeptic. Sustained disorder was not observed. Renal disorder was found on two died patients. (Hinrichs *et al*.: 1948)

A 44-year-old male taken into police custody for publish intoxication became agitated, lost consciousness, and vomited. Upon arrival in the ED he was unconscious with myoclonic jerking. Within 3 hr he was awake, alert, and reported ingesting nine yohimbine tablets and a few sprays of “pine needle oil”. A 3 oz opaque white pump spray bottle with a citrus smelling liquid reported to contain “pine needle oil” was analysed by DEA Western Labs to contain 1,4-butanediol. (Dyer *et al.*: 1997)

After one man took Thunder Nectar, he died. His wife, who also took Thunder Nectar, was unconscious for several hours but survived. “Thunder Nectar” was a brand name of product including 1,4-butanediol. (Gugliotta: 1999)

In man, it was reported that sleep is induced by intravenous administration of 30 mg/kg b.w. or by infusion of 15 to 22 mg/kg/hr for about 38 to 68 hr (initial dose: 30 mg/kg b.w.). Undesirable side-effects which may occur include restlessness and clonic spasms of the muscle of the extremities. (Toxikologische Bewertung: 1993))

Recently, FDA reported that at least three people had died and more than 100 had become ill after taking unregulated new products, which are listed as “party drugs” on internet sites, advertised in muscle-building magazines, and sold in health food stores as dietary supplements to aid in sleep. These products contain 1,4-butanediol. According to FDA, 1,4-butanediol can cause dangerously low respiratory rates, unconscious, vomiting, seizures and death. In addition, this chemical may also increase the effects of alcohol, and is even more dangerous when consumed with other depressant drugs. (FDA talk paper: 1999)

γ-Hydroxybutyric acid, a major human metabolite of 1,4-butanediol, is known as *liquid x*, *Georgia home boy*, *Goop*, *gamma-oh*, and *grievous bodily harm*. γ-Hydroxybutyric acid is a central nervous system depressant abused for its ability to produce euphoric and hallucinatory states and its alleged ability to release a growth hormone and stimulate muscle growth. Although γ-hydroxybutyric acid was originally considered a safe and "natural" food supplement and was sold in health food stores, the medical community soon became aware that it caused overdoses and other health problems. γ-

Hydroxybutyric acid can produce drowsiness, dizziness, nausea, unconsciousness, seizures, severe respiratory depression, and coma. γ-Hydroxybutyric acid can be found in liquid form or as a white powdered material. It is taken orally and is frequently combined with alcohol. Abusers include high school and college students and rave party attendees who use γ-hydroxybutyric acid for its intoxicating effects. Some body builders also abuse γ-hydroxybutyric acid for its alleged anabolic effects. Several cases have documented the use of γ-hydroxybutyric acid to incapacitate women for the commission of sexual assault. In 1990, FDA issued an advisory declaring γ-hydroxybutyric acid unsafe and illicit except under FDA-approved, physician-supervised protocols. In March 1999, the DEA recommended that Congress place γ-hydroxybutyric acid under the Controlled Substances Act. Legislation to include γ-hydroxybutyric acid in the Controlled Substances Act is currently being considered. (U.S. Department of Justice: 1999)

γ-Hydroxybutyric acid is now a Schedule 1 controlled drug. A schedule 1 controlled drug in the US is one that:

- The drug or other substance has a high potential for abuse.
- The drug or other substance has no currently accepted medical use in treatment in the United States.
- There is a lack of accepted safety for use of the drug or other substance under medical supervision.

(U.S. Department of Justice)

4.3 Initial Assessment for Human Health

Acute lethal toxicity of 1,4-butanediol is low via any administration routes. This chemical is a slight irritant to the skin, eyes and respiratory tract, but not a skin sensitizer. By oral administration, NOAEL is considered to be 100 mg/kg/day, based on the disappearance of neurotoxicity in mouse developmental toxicity study. This conclusion is confirmed by the result of an OECD combined rat study. In a 2 week inhalation study, NOAEL is considered to be 1.1 g/m^3 (6 hours/day, 5 days/week). Via an intraperitoneal route, narcotic effect was induced at more than 500 mg/kg/day. As for reproductive/developmental toxicity, a reduction in fetal body weight was only induced. But this effect was considered to be secondary to maternal toxicity. NOAELs for reproductive and developmental toxicity are considered to be the highest doses of 800 and 600 mg/kg/day, respectively. This chemical is considered not to be genotoxic, based on negative results of bacterial mutation test and chromosomal aberration test *in vitro*. This chemical seems to show a competitive inhibition of alcohol dehydrogenase and increase the toxic effect of alcohol.

From repeated dose studies, it is evident that critical effect is neurotoxicity. However, the nature of the data does not allow for the identification of the dose-response and NOAEL for this effect.

Occupational exposure

1,4-Butanediol is produced and used in a closed system at industries. As the exposure route for human may be an inhalation and skin in limited workers, there is no available data of the atmosphere concentration. The highest daily intake (combined EHE) including dermal exposure at the occupational place is calculated as 3.2 mg/kg/day as the worst case. On the other hand, the daily intake in animal inhalation study is equivalent to 134 mg/kg/day, based on the lowest NOAEL of 1.1 g/m^3 (6 hours/day, 5 days/week). Margin of safety is approx. 40. Therefore, the occupational exposure should be concerned as a human health risk although workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

Consumer exposure

In Sponsor country, consumer exposure is not expected because of its use pattern. In US, some toxic effects such as low respiratory rates, unconsciousness, vomiting, seizures and death were reported by FDA. Recently, FDA announced that the products including 1,4-butanediol was unapproved and has conducted seizures of the product to prevent the sale to consumers and any further illness or deaths (FDA talk paper: 1999). In European countries, this chemical is used as an ingredient in deodorants. Therefore, consumer exposure is expected.

Indirect exposure via environment

As for indirect exposure via environment, PEC_{local} of 1.10×10^{-3} mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as 3.67×10^{-5} mg/kg/day and 1.65×10^{-5} mg/kg/day, respectively. Since the margin of safety is very large, such as 2.73×10^{6} for drinking water and 6.06×10^{6} for fish, health risk via environment is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Exposure
The production volume of this chemical was 29,717 tones in 1993 in Japan. This chemical is used as an intermediate for resins and/or solvents in closed system, and not included in consumer products of Sponsor country. The potential environmental distribution of this chemical obtained from a generic fugacity model (Mackey level III) shows that this chemical will be distributed mostly in water (99.6 %) and partly in sediment (0.4%) when it is discharged into water. The route of occupational exposure is inhalation and skin with a limited numbers of workers. As consumer use, this chemical is used as an ingredient in deodorants in European countries, and marketed as dietary supplement in US.

Environment
1,4-Butanediol is liquid at 20 °C, and this chemical is classified as a readily biodegradable chemical (OECD 301C: 100 % after 14-day). Bioconcentration factor may be low judging from a low log P_{ow} value (0.50 at 25 °C).

The lowest acute and chronic toxicity data were 14d LC50 (>100 mg/l) of fish (Medaka; *O. latipes*) and 21d NOEC (> 85 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, because chronic toxicity data for fish were not available. Thus, PNEC of this chemical is >0.85 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 85 mg/l.

Human Health Hazards
Acute lethal toxicity of 1,4-butanediol is low via all administration routes. Major toxicity by oral administration is respiratory failure and catalepsy. This chemical is a slight irritant to the skin, eyes and respiratory tract, but not a skin sensitizer. As 1,4-butanediol is rapidly absorbed and metabolized to γ-hydroxybutyric acid in animals and humans, neurotoxic effect of 1,4-butanediol such as depression of central nervous system is considered to be caused by the metabolite, γ-hydroxybutyric acid. 1,4-Butanediol seems to show a competitive inhibition of alcohol dehydrogenase and increase the toxic effect of alcohol.

In an OECD combined repeat dose and reproductive/developmental screening toxicity test (TG 422), rats were administered by gavage at doses of 200, 400 and 800 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. Neurobehavioral toxicity (i.e. hyperactivity and coma after hypoactivity and recumbency) and pathological changes (diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder) were observed. The transient hyperactivity only just after administration was observed at the lowest dose of 200 mg/kg/day. This neurotoxicity in dams was also observed in developmental toxicity study of mice at doses of 300 and 600 mg/kg/day by gavage during gestational days 6-15 but not at 100 mg/kg/day. This study was conducted by NTP test guideline under GLP. Therefore NOAEL of 100 mg/kg/day for oral repeated toxicity is sufficiently reliable.

In a 2 week inhalation rat study at 1.1 g/m^3 (6 hours/day, 5 days/week), no changes including neurotoxicity were observed. Therefore, 1.1 g/m^3 is considered to be inhalation NOAEL. Repeated intraperitoneal administration induced narcotic effect at more than 500 mg/kg/day, but NOAEL was not established.

From repeated dose studies, it is evident that critical effect is neurotoxicity. However, the nature of the data does not allow for the identification of the dose-response and NOAEL for this effect.

As for reproductive toxicity, a reduction in fetal body weight was observed at the above OECD combined repeat dose and reproductive/developmental screening toxicity test (TG 422) of rats but this effect was considered to be secondary to maternal toxicity. NOAEL for reproductive toxicity is the highest dose of 800 mg/kg/day. In the developmental toxicity study of mice at doses of 100, 300 and 600 mg/kg/day described above, the only definitive expression of developmental toxicity was a reduction in average fetal body weight at doses of 300 and 600 mg/kg/day (92% and 83% of control weight, respectively). However, this effect against fetus was considered to be secondary to maternal toxicity. No teratogenicity was observed at any doses. Thus, 600 mg/kg/day is the developmental NOAEL. Genotoxicity of this chemical may be negative because of neither bacterial mutation in *S. Typhimurium* TA100, TA98, TA1535, TA1537, and *E.coli* WP2 *uvr*A with and without metabolic activation (OECD TG 471 and 472), nor chromosomal aberration *in vitro* in CHL/IU cells with or without metabolic activation system OECD TG (473).

5.2 Recommendations

Human health

Further exposure information should be collected in each member countries because of its metabolism to γ-hydroxybutyric acid and observed neurotoxicity**.**

6. REFERENCES

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Appendix 1

Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local}\ (mg/L) = \frac{Co\ Q + Cs\ Qs}{Q + Qs} \quad (1)$$

Where
Co: Concentration of pollutant in upper stream of release point (mg/L)
Cs: Concentration of pollutant in effluent (mg/L)
Q: Flow rate of river (m^3/day)
Qs: Flow rate of effluent released into river (m^3/ day)

At the equation (1), when Co can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = Cs/C = (Q + Qs) / Qs \quad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow late} / 2.5 \quad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendner's equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

1 It is adopted large area of sea or lake.
2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
5 There is not any effect of tidal current.
6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r))\left(1 - \exp\left(-\frac{Q_s}{\theta\, d\, p}\left(\frac{1}{x} - \frac{1}{r}\right)\right)\right) + C(r) \qquad (4)$$

Where
C (x): Concentration of pollutant at distance x (m) from release point
Cs: Concentration of pollutant in effluent
C (r): Concentration of pollutant at distance r (m) from release point
Qs: Flow rate of effluent (m^3/day)
θ : Opening angle of seacoast (rad.)
d: Thickness of diffusion layer (m)
P: Diffusion velocity (m/day) (1.0 $\pm$ 0.5 cm/sec)

When C(x) is 0 at r = ∞ and density stratification is ignored for simplification, Joseph-Sendner's equation (4) is simplified to equation (5)

$$C(x) = C_s\left(1 - \exp\left(-\frac{Q_s}{\theta\, d\, p\, x}\right)\right) \qquad (5)$$

Because of $Q_s/\theta\, d\, p\, x \ll 1$ except vicinity of release point, dilution factor in distance x from release point R(x) can be shown with equation (6).

$$R(x) = C_s/C(x) = \theta\, d\, p\, x/Q_s \qquad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

P = 1 cm/sec (860 m/day)
θ = 3.14
d = 10 m
x = 1000 m

$$R = 2.7 \times 10^7/Q_s \qquad (7)$$

Qs: volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER
ON THE HPV PHASE 4 CHEMICAL

1,4-Butanediol

CAS No. 110-63-4

Sponsor Country: Japan

DATE: December 1, 1999

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1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A. CAS number** 110-63-4

B. Name *(IUPAC name)*

***C. Name** *(OECD name)* 1,4-Butanediol

†D. CAS Descriptor

E. EINECS-Number 203-786-5

F. Molecular Formula $C_4H_{10}O_2$

***G. Structural Formula**

$HO\text{-}CH_2CH_2CH_2CH_2\text{-}OH$

H. Substance Group

I. Substance Remark

J. Molecular Weight 90.12

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)
Environmental Agency (EA)
Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
Director, Second International Organization Bureau
Ministry of Foreign Affairs

Address:

Street: 2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100 Japan
Tel: 81-3-3581-0018
Fax: 81-3-3503-3136

C. Name of responder

Name: 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 *(at 20°C and 1.013 hPa)*

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

C. Purity:

98.0%

1.2 SYNONYMS

1,4-Butylene glycol; 1,4-Dihydroxybutane; Tetramethylene glycol; Butanediol; Butane-1,4-diol; 1,4-Tetramethylene glycol; Butylene glycol; Tetramethylene-1,4-diol

1.3 IMPURITIES

None

1.4 ADDITIVES

None

*1.5 QUANTITY

Remarks: 29,717 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

R22: Harmful if swallowed
R36/38: Irritating to eyes and skin

*1.7 USE PATTERN

A. General

	Type of Use:	**Category:**
	main	Intermediate
	industrial	Intermediate in closed system
	use	Intermediate for resins

Remarks: None
Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

*** 1.9 SOURCES OF EXPOSURE**

In Japan, 1,4-butanediol is produced in 3 companies.

Source: Media of release: River
Quantities per media: 4 tonnes/year (one company)
Remarks:
Reference: MITI, Japan

2. PHYSICAL-CHEMICAL DATA

***2.1 MELTING POINT**

Value: 20 °C
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: MITI, Japan

***2.2 BOILING POINT**

Value: 235 °C
Pressure: at 1,018 hPa
Decomposition: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks:
Reference: KAGAKU DAIJITEN (Chemical Dictionary)

***2.4 VAPOUR PRESSURE**

Value: 1.9×10^0 Pa
Temperature: 25 °C
Method: calculated **[ ]**; measured **[X]**
OECD TG 104
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.5 %
Remarks:
Reference: MITI, Japan

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

Log Pow: 0.50
Temperature: 25 °C
Method: calculated **[ ]**; measured **[** X **]**
OECD TG 107
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.5 %
Remarks:
Reference: MITI, Japan

***2.6 WATER SOLUBILITY**

A. Solubility

Value:	> 100 g/L
Temperature:	25 °C
Description:	Miscible **[ ]**; Of very high solubility **[X]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method:	OECD TG 105
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99.5 %
Remarks:	
Reference:	MITI, Japan

B. pH Value, pKa Value

No ionizable Functional Group

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1 STABILITY

*3.1.1 PHOTODEGRADATION

Type:	Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source:	Sun light **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum:	
Relative intensity:	
Spectrum of substance:	
Concentration of Substance:	
Temperature:	
Direct photolysis:	
Half life:	
Degradation:	
Quantum yield:	
Indirect Photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	
Rate constant (radical):	16 * 10^{-12} cm3/molecule*sec
Degradation:	
Method:	calculated **[X];** measured **[ ]** Other (calculated, according to Atkinson 1986)
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Test substance:	
Remarks:	Half-life of 24 hour is calculated based on the rate constants (16 * 10^{-12} cm3/molecule*sec) by using the concentration of OH-radicals of 500000 molecule/cm3 in atmosphere
Reference:	Atkinson, R., 1988.

*3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life:	Stable at pH 4, 7, 9 at 25 °C

Method: OECD TG 111
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.5 %
Remarks:
Reference: MITI, Japan

***3.2 MONITORING DATA (ENVIRONMENTAL)**

(a)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (river)
Results: ND (Detection limits: 0.002 mg/l) in 1 area in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

(b)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (estuary)
Results: ND (Detection limits: 0.002 mg/l) in 2 areas in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

(c)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Surface water (sea)
Results: ND (Detection limits: 0.002 mg/l) in 5 areas in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

(d)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Sediment (river)
Results: ND (Detection limits: 0.09 mg/kg-dry) in 1 area in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

(e)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Sediment (estuary)
Results: ND (Detection limits: 0.09 mg/kg-dry) in 2 areas in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

(f)
Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[x]**
Media: Sediment (sea)
Results: ND (Detection limit: 0.09 mg/kg-dry) in 5 areas in Japan as of 1986
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1987)

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

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

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

Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**; Other (measurement)**[ ]**

Results:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.4 %	0.0 %	0.0 %
Water	47.7 %	99.6 %	41.4 %
Soil	51.6 %	0.0 %	58.4 %
Sediment	0.2 %	0.4 %	0.2 %

Remarks: Appendix 1
Reference: MITI. Japan

*3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 83 % by BOD after 14 days
94 % by TOC after 14 days
100 % by GC after 14 days
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Method: OECD TG 301C
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity > 99 %
Reference: MITI, Japan

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Type of test: static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**
open-system **[X]**; closed-system **[ ]**
Species: Medaka (*Oryzias latipes*)
Exposure period: 96 h
Results: LC_{50} (96h) > 100 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 203 (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: >98 %
Remarks: Groups of ten Medaka were placed to nominal concentration of 100 mg/l and dechlorinated tab water as control. The LC_{50} (96h) was over 100 mg/l.

Measured concentrations at the start of exposure and after 48 h when test water was renewed were 85.6 and 99.9% of the nominal concentration, respectively.
Reference: Environment Agency of Japan (1996)

(b) Type of test: static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**
open-system **[X]**; closed-system **[ ]**

Species:	Medaka (*Oryzias latipes*)
Exposure period:	14 d
Results:	$LC_{50\ (14d)} > 100$ mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203 (1992).
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: > 98%
Remarks:	Groups of ten Medaka were exposed to nominal concentration of 100 mg/l and dechlorinated tap water as control. Measured concentrations at the start of exposure, after 7 and 14 days were 93.0, 97.2 and 87.2% of the nominal concentration, respectively. Test water was exchanged with fresh one every two days.
Reference:	Environment Agency of Japan (1996)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	48 h
Results:	$EC_{50\ (48\ h)} > 1000$ mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: > 98 %
Remarks:	20 daphnids (4 replicates of 5 test organisms) were exposed to nominal concentration of 1000 mg/l. M4 medium was used for the test. Measured concentration after 48 h was grater than 80% of the nominal concentration.
Reference:	Environment Agency of Japan (1995)

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:	*Selenastrum capricornutum* ATCC 22662	
Endpoint:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**	
Exposure period:	72 h	
Results:	Biomass	$EC_{50\ (72h)} > 1000$ mg/l
	(Endpoint)	NOEC > 1000 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**	
Method:	OECD TG 201 (1984)	
	open-system **[X]**; closed-system **[ ]**	
GLP:	Yes **[X]** No **[ ]** ? **[ ]**	
Test substance:	As prescribed by 1.1 - 1.4, purity: > 98 %	
Remarks:	Static test. The EC_{50} or NOEC were evaluated depended on the nominal concentration, because measured concentration after 72h was grater than 80% of the nominal concentration. No solubilizer was used.	
Reference:	Environment Agency of Japan (1995)	

4.4 TOXICITY TO BACTERIA

No data

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data

(*) 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Endpoint:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period:	21 d
Results:	Reproduction rate: EC_{50} (21 d) > 85 mg/l *(Endpoint)* NOEC > 85 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202(1984)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: > 98 %
Remarks:	40 daphnids (4 replicates of 10 daphnids) were exposed to nominal concentration of 100 mg/l. M4 medium was used for the test. Toxicity values were calculated based on the mean measured concentration (85% of the nominal concentration; 64.1 to 92.5 %).
Reference:	Environment Agency of Japan (1995).

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

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

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Wistar Imp:DAK rats
Value:	Male: 1,830 mg/kg b.w. Female: 2,000 mg/kg b.w. Discriminating dose: 1,500 – 2,500 mg/kg b.w.
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Purity: More than 98 %
Remarks:	Deaths occurred within 48 hours after the administration. As the most common signs of toxicity, irregular decreased respiration and catalepsy were observed. Gross pathological findings in dead animals included a fluid-filled gastrointestinal tract and congestion of internal organs. The additional test was performed at a dose of 1,800 mg/kg b.w. to assess pathological lesion 48 hours and 14 days after administration. Histological change was observed in liver and kidneys.
Reference:	Jedrychowski *et al*.: 1990a

(b)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Albino rats
Value:	1,525 mg/kg b.w. Discriminating dose:
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Purity: Unknown
Remarks:	The animals died on the 1st - 2nd day. The clinical pattern of acute poisoning developed 10 – 15 minutes after the administration. The characteristic feature was marked lack of vitality, lateral posture, and marked hyperemia of the visible mucosa. Post-mortem investigation revealed marked hyperemia in all the internal organs and in the brain.
Reference:	Knyshova: 1968

(c)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	White mice
Value:	2,062 mg/kg b.w. Discriminating dose:
Method:	Other
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Purity: Unknown
Remarks:	The animals died on the 1st - 2nd day. The clinical pattern of acute poisoning developed 10 – 15 minutes after the administration. The characteristic features were marked lack of vitality, lateral posture, and marked hyperemia of the visible mucosa. Post-mortem investigation revealed marked hyperemia in all the internal organs and in the brain.
Reference:	Knyshova: 1968

(d)

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rabbits
Value:	2,531 mg/kg b.w.

Discriminating dose:
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Remarks: The animals died on the 1st - 2nd day. The clinical pattern of acute poisoning developed 10 – 15 minutes after the administration. The characteristic features were marked lack of vitality, lateral posture, and marked hyperemia of the visible mucosa. Post-mortem investigation revealed marked hyperemia in all the internal organs and in the brain.
Reference: Knyshova: 1968

(e)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Guinea pigs
Value: 1,200 mg/kg b.w.
Discriminating dose:
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Remarks: The animals died on the 1st - 2nd day. The clinical pattern of acute poisoning developed 10 – 15 minutes after the administration. The characteristic features were marked lack of vitality, lateral posture, and marked hyperemia of the visible mucosa. Post-mortem investigation revealed marked hyperemia in all the internal organs and in the brain.
Reference: Knyshova: 1968

5.1.2 ACUTE INHALATION TOXICITY

(a)
Type: LC_0 **[X]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain: Wistar rats
Exposure time: 4 hours
Value: 5.1 g/m^3 (as a liquid aerosol)
Method: OECD Guideline 403 "Acute Inhalation Toxicity"
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 99.6 %
Remarks: There were some slightly respiratory clinical signs (accelerated respiration, shallow respiration etc.) during and after exposure. From day 1 of the observation period (14 days), these signs could not be detected. On gross-pathological examination, no abnormalities could be detected.
Reference: BASF: 1991

(b)
Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[X]**; Other **[ ]**
Species/strain: Crl:CD-BR rats (male)
Exposure time: 4 hours
Value: 15 g/m^3
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: more than 99.7 %
Remarks: Male rats were exposed nose-only to 4.6, 9.4, or 15.0 g/m^3. Survivors were killed after 14-day observation period.

All rats survived at 4.6 or 9.4 g/m^3, but one of ten rats died 1-day post exposure at 15 g/m^3. After exposure, rats at 4.6 and 9.4 g/m^3 were lethargic

with labored breathing. At 15.0 g/m^3, red discharge was observed in the perineal area. A few rats at 9.4 and 15.0 g/m^3 had lung noise and dry red nasal discharge lasting 1-9 days post-exposure. Rats in all treated groups displayed slight (4.6 g/m^3) to severe (150 g/m^3) weight loss for 24 h post exposure, followed by resumption of normal rate of weight gain.

Reference: Kinney *et al.*: 1991

5.1.3 ACUTE DERMAL TOXICITY

Type: LD_0 **[X]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Wistar Imp:DAK rats (female)
Value: 5,000 mg/kg b.w.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Remarks: The sides and dorsum of all rats were clipped. Test material was applied to the intact dorsum of the animals as an undiluted liquid and the application sites were covered with gauze patches and wrapped with impervious plastic sleeves. 24 hours after dosing, the sleeves were removed. Daily observation for mortality and toxic signs was made and the rats were killed and necropsied either 48 hours or 14 days after application.

Histopathological changes were limited to the skin and liver.
Reference: Jedrychowski *et al*.: 1990a

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Wistar albino rats
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time:
Value: 11.87 - 11.90 mmol/kg (95 % confidence limit, calculated as about 1070 mg/kg)
Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Remarks: 1,4-Butanediol at 8.90 – 17.80 mmol/kg was administered to rats (5 groups of 6 rats). LD_0 and LD_{100} were 8.90 and 17.80, respectively.

At 8.90 mmol/kg, there was a characteristic hypnotic state, with loss of the righting reflex and maintained muscle tone, after a latency of about 20 min after injection. Increasing the dose produced an increase in the depth of hypnosis together with a marked bradycardia, analgesia and laboured respiration. Death appeared to be due to respiratory failure.

Administration with 1,4-butanediol (17.80 mmol/kg) after treatment with pyrazole (2.9 mmol/kg, i.p.), an inhibitor of liver dehydrogenase, induced neither death nor behavioral changes.
Reference: Taberner and Pearce: 1974

(b)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rats
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**

Exposure time:
Value: 1,330 mg/kg
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks:
Reference: Zabik *et al.*: 1974

(c)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mice
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time:
Value: 1,660 mg/kg
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks:
Reference: Holman *et al.*: 1979

(d)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mice
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[X]**; other **[ ]**
Exposure time:
Value: 2,000 mg/kg
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks:
Reference: Dominguez-Gil and Cadorniga: 1971

(e)
Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mice
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[X]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time:
Value: 1,000 mg/kg
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks:
Reference: Dominguez-Gil and Cadorniga: 1971

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)
Species/strain: Rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**

Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Remarks: Repeated application to both intact and abraded skin resulted in no appreciable irritation and no evidence of absorption of acutely toxic amounts.
Reference: Knyshova: 1968

(b)
Species/strain: White Vienna rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Remarks: Fur from the side-areas of the trunk of all animals was removed by clipping and shaving. The gauze patches with undiluted 1,4-butanediol were applied to the intact and abraded skin animals. Adjacent area of untreated and water treated skin of each animal served as a control. The patches were covered with plastic foil and protected by means of a suitable occlusive dressing for the 24 hours exposure period. Observation for dermal irritation was made 1, 24, 48 and 72 hours after patch removal.

No reaction on the intact and abraded skin.
Reference: Jedrychowski *et al.*: 1990a

(c)
Species/strain: White Vienna rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Remarks: The internal areas of the right ears of rabbits were painted with either 100 % or 50 % of 1,4-butanediol in water for 10 consecutive days. The left ear of each rabbit painted with water served as a control. Observation was made the day after painting.

After 10 days of exposure period, a minimal reddening was observed in 100 % treated group.
Reference: Jedrychowski *et al.*: 1990a

5.2.2 EYE IRRITATION/CORROSION

(a)
Species/strain: New Zealand White rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**

Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Remarks: 1,4-Butanediol was administered to four rabbits as a single dose of 0.1 mL, which was placed in the conjunctival sac of the right. The unexposed rabbits served as a concurrent control. The observation was made at intervals of 1, 24, 48 and 72 hours post-dosing.

Slight reddening of the conjunctives and small amounts of discharge were observed in all rabbits 1 hour after ocular application. The changes diminished after 24 and 48 hours. No abnormalities were observed thereafter.
Reference: Jedrychowski *et al.*: 1990a

(b)
Species/strain: Rabbits
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**;
Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**;
Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Unknown
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks: Very slight conjunctival irritation but no corneal injury
Reference: Rowe and Wolf: 1982

5.3 SKIN SENSITISATION

Type: Maximization test
Species/strain: Hartley guinea pigs
Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Remarks: In induction procedure, 1,4-butanediol was applied at a concentration of 10 % (intradermal injections) and 30 % (topical application). The challenge procedure was done with 10 % and 30 % 1,4-butanediol.)

No allergic contact dermatitis
Reference: Jedrychowski *et al.*: 1990a

*5.4 REPEATED DOSE TOXICITY

(a)
Species/strain: Rats/ Wistar Imp:DAK
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (by gavage)
Exposure period: 28 days
Frequency of treatment: Daily
Post exposure observation period: 1 day
Dose: 5, 50, 500 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: Male: 50 mg/kg/day
Female: 50 mg/kg/day

LOAEL: Male: 500 mg/kg/day
Female: 500 mg/kg/day

Results: There were no changes in body weight, food consumption, and absolute and relative organ weights. A statistically significant increase in activities of sorbitol dehydrogenase and alanine aminotransferase was observed at 500 mg/kg/day in males. In hematological examination, although there were some statistically significant changes (decrease in red blood cell and platelet counts, and increase in the erythrocytic MCV, MCH, and MCHC values, etc.), these changes were not dose-related and the values remained within normal physiological limits. Proliferation of bile ducts and periportal infiltrations with fibroblasts and mononuclear cells were found in liver of treated animals. Frequencies of such changes were 0/5, 3/5, 1/5, and 3/5 in males, and 1/5, 1/5, 3/5, and 4/5 in females, respectively for control, low-, mid-, and high-dose groups. Incidence of proliferation of bile ducts was statistically significance at 500 mg/kg/day only in the case where both sexes were jointly taken for comparison.

Five of eight animals administered with 1,4-butanediol were examined histopathologically.

Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: More than 98 %
Reference: Jedrychowski *et al.*: 1990b

(b)
Species/strain: Rats/Crj; CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (by gavage)
Exposure period: Males: 42 days
Females: from 14 days prior to mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period: 1 day
Dose: 200, 400, 800 mg/kg/day (in distilled water)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
LOAEL: Male: 200 mg/kg/day
Female: 200 mg/kg/day

Results: Acute and transient toxic signs in central nervous system were observed after daily administration of 1,4-butanediol in both sexes, and severity of the sign increased with dosage levels. The transient hyperactivity only just after administration was observed at 200 mg/kg/day. At 400 mg/kg, activities were rather suppressed than increased although hyperactivity was also observed after a few doses. At 800 mg/kg, toxic signs observed were more severe and some animals were even comatose after showing hypoactivity and recumbency. By 5 hours after dosing these signs disappeared and animals recovered to normal. Body weight gains were suppressed at 400 and 800 mg/kg during the early period of administration. The weight gains were not further suppressed thereafter, the difference in body weight produced during the early period of administration remained until termination of the study. Food consumption also decreased accordingly. In hematological and blood chemistry findings of males, there were slightly but statistically significant and dose-related decrease of blood glucose at all treated groups. At terminal necropsy, no compound-related lesions were noted macroscopically. In the histopathological examination, diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder were observed in the 400

and 800 mg/kg groups, but there were no significant changes in other tissues examined, such as liver, kidney, and thymus.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test (OECD TG 422)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 98.0 %
Reference: MHW, Japan (1999)

(c)
Species/strain: Rats
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Inhalation
Exposure period: 4 months
Frequency of treatment: 2 hours/day, daily
Post exposure observation period:
Dose: 1.5 - 2 g/m^3 (finely dispersed aerosol, calculated daily dose: 85 - 110 mg/kg/day (0.29 m^3/day, 0.425 kg))
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
LOAEL: Male: 1.5 g/m^3 (85 mg/kg/day)
Results: Clinical symptoms were not observed at the beginning of the study. However animals became inactive and sleepy condition after 3 or 4 weeks, and these were reversible within 10 to 20 minutes after the exposure. Body weight, hematogenesis and neuromuscular response were not changed. Histopathological examination revealed a lot of pulmonary emphysema and the mild lung edema. In a few animals, there were the inflammatory changes of single alveolar cell and weak hyperplasia of alveolar septum with proliferation of lymphocytes and histiocytes. There were no-treatment related pathological changes in any other organs.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Reference: Stasenkova: 1965

(d)
Species/strain: Rats
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Inhalation
Exposure period: 4 months
Frequency of treatment: 2 hours/day, 6 days/week
Post exposure observation period:
Dose: 0.3 - 0.5 g/m^3 (calculated daily dose: 15 - 24 mg/kg/day (0.29 m^3/day, 0.425 kg))
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: Male: 0.5 g/m^3 (24 mg/kg/day)
Results: No clinical signs of toxicity were observed following exposure to 1,4-butanediol. Body weight, function of nervous system (neuromuscular response) and hemogenesis as well as liver and kidney function were not changed.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Reference: Stasenkova: 1965

(e)
Species/strain: Rats/ Crl: CD
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Inhalation (nose only exposure to aerosol)
Exposure period: 2 weeks
Frequency of treatment: 6 hours/day, 5 days/week (5 exposure days, 2 rest days, 5 exposure days)
Post exposure observation period: 0 or 2 weeks
Dose: 0.20, 1.1, 5.2 g/m^3 (calculated daily dose: 24, 134, 634 mg/kg/day (0.29 m^3/day, 0.425 kg))
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: Male: 1.1 g/m^3 (134 mg/kg/day)
Female: 1.1 g/m^3 (134 mg/kg/day)
LOAEL: Male: 5.2 g/m^3 (634 mg/kg/day)
Female: 5.2 g/m^3 (634 mg/kg/day)
Results: Mean body weights for rats exposed to 5.2 g/m^3 were significantly lower than the controls from the third exposure day to 4 days post-exposure. There was a significant decrease in heart weights after ten exposures at 5.2 g/m^3. In hematological examination, there was a significant increase in erythrocyte counts and hematocrits, and a significant decrease in serum cholesterol concentrations when sacrificed immediately after the tenth exposure to 5.2 g/m^3. Urine studies failed to reveal any significant differences between the test and control rats. Pathological examination showed slight atrophy of lymphoid cells in the thymus in 3/5 rats exposed to 5.2 g/m^3. These changes at 5.2 g/m^3 returned to normal during the recovery period. No adverse effects were observed in rats exposed to either 0.20 or 1.1 g/m^3.
Method: Other
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: more than 99.7 %
Reference: Kinney *et al.*: 1991

(f)
Species/strain: Rats/Sprague-Dawley
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: i.p.
Exposure period: 10 days
Frequency of treatment: Daily
Post exposure observation period:
Dose: 500, 1,000 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: 500 mg/kg/day
LOAEL: 1,000 mg/kg/day
Results: No death and no significant depression of body weight gain were shown at 500 mg/kg/day. With slightly depressed weight gain, plasma and liver free fatty acids and triglycerides were slightly changed at 1000 mg/kg/day.
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Reference: Zabik *et al.*: 1973

(g)
Species/strain: Rats/Sprague-Dawley
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: i.p.

Exposure period: 14 days
Frequency of treatment: Daily
Post exposure observation period:
Dose: 500, 1,000 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: Not published
Results: Narcotic effect was observed but it reduced in progress of the study. Liver TG value was not changed.

There was no data on doses, at which these changes occurred.
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Reference: Zabik *et al.*: 1974

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537
Escherichia coli WP2 *uvr*A
Concentration: -S9: 0, 313, 625, 1250, 2500, 5000 μg /plate
+S9: 0, 313, 625, 1250, 2500, 5000 μg /plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone.
Results:
Cytotoxicity conc: Toxicity was not observed at 5000 μg/plate in five strains with or without an S9 mix.
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG (471 and 472)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 98.0 %
Remarks:
Reference: MHW, Japan (1997)

B. NON-BACTERIAL IN VITRO TEST

(a)
Type: Chromosomal aberration test (Metaphase chromosome analysis)
System of testing: V79 Chinese hamster lung cell
Concentration: 400, 3,000, 5,000 μg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254
Results:
Cytotoxicity conc:
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: OECD Genetic Toxicology: In vitro Mammalian Cytogenetic Test (OECD TG 473)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 99.7 %
Remarks: V79 cells, cultured on microscopic slides, were exposed to 1,4-butanediol for 26 and 41 hours. After the exposure, cells were arrested in metaphase by 2 hours treatment with Colcemid. After hypotonic treatment, cells were fixed and Giemsa stained. For each experimental point, duplicate cultures (100 metaphases/culture) were evaluated.
Positive control: Cyclophosphamide (2 µg/ml with S9 mix)
Mitomycin C (0.02 µg/ml without S9 mix)
Reference: Hüls AG: 1993a

(b)
Type: Mammalian cell gene mutation assay (HPRT test)
System of testing: Chinese hamster ovary (CHO) cell
Concentration: 20, 60, 200, 600, 2,000 µg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with Aroclor 1254
Results:
Cytotoxicity conc:
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: OECD Genetic Toxicology: In vitro Mammalian Cell Gene Mutation Tests (OECD TG 476)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 99.7 %
Remarks: The ability to induce forward mutation at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus was examined.

In a third experiment of three experiments performed, although an additional concentration of 5,000 µg/ml was employed, in this part of the study the negative controls were higher than normal.
Negative control: culture medium
Positive control: 3-Metylcholanthrene (with S9 mix)
Ethyl methane sulfonate (without S9 mix)
Reference: Hüls AG: 1993b

(c)
Type: Chromosomal aberration test
System of testing: CHL/IU cell
Concentration: -S9 (continuous treatment): 0, 0.23, 0.45, 0.90 mg/ml
-S9 (short-term treatment): 0, 0.23, 0.45, 0.90 mg/ml
+S9 (short-term treatment): 0, 0.23, 0.45, 0.90 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone.
Results:
Cytotoxicity conc: Cytotoxic effects were not seen under the conditions in this experiment.
Precipitation conc:
Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG (473).
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 98.0 %
Remarks:
Reference: MHW, Japan (1997)

*** 5.6 GENETIC TOXICITY IN VIVO**

Type: Drosophila SLRL test
Species: Drosophila melanogaster
Sex: Male
Route of administration: Oral (feed)
Exposure period: 3 days
Doses: 0.3814 %
Results: Negative
Method: Unknown
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: Unknown
Remarks: Lee W.R. *et al.* (1983) commented that compounds that could not be classified as positive or negative for mutagenic activity in the Drosophila Sex-linked Recessive Lethal Test because of inadequate Sample size.
Reference: Roehrborn: 1959

5.7 CARCINOGENICITY

No data

***5.8 TOXICITY TO REPRODUCTION**

Type: Fertility **[ ]**; One-generation study **[ ]**; Two-generation study **[ ]**; Other **[X]**
Species/strain: Rats/Crj: CD (SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: Male: For 2 weeks prior to mating and 2 weeks of mating
Female: For 2 weeks prior to mating, 2 weeks of mating and throughout pregnancy until day 3 postpartum
Frequency of treatment: Daily
Post exposure observation period:
Premating exposure period: Male: 14 days, Female: 14 days
Duration of the test:
Dose: 200, 400, 800 mg/kg/day (in distilled water)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; Corn oil
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL Parental: Male; 800 mg/kg, Female; 800 mg/kg
NOAEL F1 Offspring: 800 mg/kg
Results: The parental animals exhibited no alteration in reproductive parameters including the copulation index, fertility index, gestation length, numbers of corpora lutea or implantation, implantation index, gestation index, delivery index, and behavior at delivery and lactation. Although neither the pup viability nor the incidence of morphological abnormalities was changed by administration of the compound, pup body weight was slightly but significantly decreased in the 800 mg/kg group.

This change was considered to be secondary to maternal toxicity (reduced food consumption and body weight gain).

Method: OECD Combined Repeat Dose and Reproductive Toxicity Screening Test (TG 422)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: 98.0 %
Remarks:
Reference: MHW, Japan (1999)

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Mice/ Swiss (CD-1)
Sex: Female **[X]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral (gavage)
Duration of the test: On days 6 through 15 of gestation
Exposure period: 10 days
Frequency of treatment: Daily
Dose: 100, 300, 600 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**; Corn oil
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL Maternal Toxicity: 100 mg/kg
NOAEL Fetal Toxicity: 600 mg/kg/day
NOAEL Teratogenicity: 600 mg/kg/day
Results: On days 17, implant survival, fetal weight, sex and morphological development (external, visceral and skeletal) were examined. There were no maternal deaths in this study. No maternal or developmental effects were observed at the low dose. Dams (60-100 %/group/day) at the mid and high doses exhibited symptoms of central nervous system intoxication (hypoactivity, immobility, loss of righting reflex and/or prone posture) during the first 4 hr following daily administration. Maternal effects at the mid and high doses also included reduced food intake (treatment and post treatment periods), reduced body weight, and reduced weight gain (treatment period, gestation period and corrected weight gain). The only definitive expression of developmental toxicity was a reduction in average fetal body weight at the middle and high doses (92% and 83% of control weight, respectively).

This effect against fetus is considered to be secondary to maternal toxicity.

Method: RTI Master Protocol No. 360/NTP Protocol No. NTP-90-CTER-133
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Purity: >99 % (Aldrich Chemical Co.)
Remarks:
Reference: Price *et al.*: 1993

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

(a)
Type: Neurotoxicity
Result: The animals at 30 mg/kg lagged with respect to the appearance and fixation of the reflex and had a longer latent period before responding to the bell. The phase states in these animals increased by 28 %. During exposure, excited reduced activity of blood cholinesterase, a change in the ratio of the protein fractions of blood serum and a decreased content of SH groups in

whole blood were induced at 30 mg/kg. At the end of exposure, there was a significant decrease in choline esterase activity and liver glycogen, in SH groups in the gray matter of the brain and vitamin C in the organs, and an increase in the activity of blood serum transaminases in animals at 30 mg/kg. At 3.0 mg/kg and 30 mg/kg, significant increase in the autodiffusion coefficient of tissue fluid was observed in liver and brain (by 19-31 %), apparently owing to variation in the permeability of cell membranes. In morphological examination, there were reduced content of Nissl bodies and the growth of glial elements in the cerebral tissue, fatty dystrophy and areas of sclerotic growth in liver and patchy hyperemia in the other organs at 30 mg/kg. At 3.0 mg/kg, morphological changes observed were regarded as incipient or liminal.

Remarks: The six months long-term experiment was carried out after preliminary tests for their ability to form conditioned reflexes in order to reveal the background of their physiological and biochemical reactions. Male rats (6 animals/group) received 0.25, 3.0, 30 mg/kg of 1,4-butanediol (no information on exposure route). One more group was served as a control (no more data). The biochemical indices and the state of conditioned reflexes were studies on identical animals.

Reference: Knyshova: 1968

(b)

Type: Neurotoxicity

Result: No clinical and pathological changes were observed in central and peripheral nervous systems.

Remarks: Sprague-Dawley rats were given 0 % (vehicle) or 0.5 % of 1,4-butanediol in drinking water (approx. 508 mg/kg/day) daily for 10 days. Examination was conducted only in nervous system.

Reference: Spencer *et al.*: 1978

(c)

Type: Effect on body temperature

Result: A fall in body temperature of 1.0 - 2.0 °C occurred about 0.5 to 4 hours after administration of 1,4-butanediol, when the loss of righting reflex was induced. This fall can be considered to be the results of the depressant action of the drugs, although a direct central hypothermic action cannot be ruled out.

Remarks: 1,4-Butanediol (500 mg/kg) was administered intraperitoneally to Wistar albino rats.

Reference: Taberner and Pearce: 1974

(d)

Type: Interaction with ethanol

Result: Behavioral, electrical and biochemical studies in rats suggest that the effects of 1,4-butanediol are indeed mediated by γ-hydroxybutyric acid. Further, ethanol appears to block conversion of 1,4-butanediol to γ-hydroxybutyric acid.

Remarks: Investigation was conducted on the interaction of 1,4-butanediol with ethanol and the involvement of the major, γ-hydroxybutyric acid in the ability of 1,4-butanediol to produce behavioral and EEG changes in rat as well as the toxic side effects of 1,4-butanediol.

Reference: Poldrugo and Snead: 1984

(e)

Type: Interaction with ethanol

Result: The simultaneous administration of ethanol increased a concentration of 1,4-butanediol in tissue, the mortality rate and tissue damage in rats. Elimination from liver was so rapid that tissue concentration reached to detection limit after 9 and 24 hours with and without simultaneous administration of ethanol, respectively.
Remarks: 1,4-butanediol (1,000 mg/kg) was administered orally to rats.
Reference: Poldrugo *et al*.: 1985

(f)
Type: Interaction with ethanol
Result: The enzymatic reaction responsible for the conversion of 1,4-butanediol to γ-hydroxybutyric acid and the interaction of ethanol with this conversion in brain and liver were examined. The enzyme responsible for this reaction in liver appeared to be alcohol dehydrogenase. In both tissues, there was a competitive inhibition by ethanol of the conversion of 1,4-butanediol to γ-hydroxybutyric acid with an apparent Ki of 6.5×10^{-3} M in brain and 2.7×10^{-3} M in liver.
Remarks:
Reference: Poldrugo and Snead: 1986

B. Toxicodynamics, toxicokinetics

(a)
Type: Metabolism
Result:
Remarks: According to the authors, 1,4-butanediol was rapidly absorbed and metabolized to γ-hydroxybutyric acid in animals and humans. The primary metabolite was further converted to succinic semialdehyde and succinic acid, which entered the tricarboxylic (citric) acid cycle. The ultimate metabolite was carbon dioxide.
Reference: NTP working group: 1996

(b)
Type: Metabolism
Result: Small amounts of succinic acid were found in the urine of rabbits, which had been fed a diet containing the test substance.
Remarks:
Reference: Patty: 1994

(c)
Type: Distribution
Result: 72 hours after administration of 1-(^{14}C)-1,4-butaneciol, a total of 2.28% of the dose remained in the carcass, with the largest amounts present in the liver, muscle, and skin. No evidence of bioaccumulation was found in any tissue.
Remarks: 1-(^{14}C)-1,4-butaneciol was administered at doses of 4, 40, 120, or 400 mg/kg to male Fischer 344 rats.

According to the authors, these results suggested that the test substance was rapidly metabolized and excreted.
Reference: NTP working group: 1996

(d)
Type: Distribution and elimination

Result: 72 minutes after administration, 1,4-butanediol was found at 50 - 90 μg/g tissue in brain, liver and kidneys. Elimination from liver was so rapid that tissue concentration reached to detection limit after 24 hours.
Remarks: 1,4-butanediol (1,000 mg/kg) was administered orally to rats.
Reference: Poldrugo *et al*.: 1985

(e)
Type: Excretion
Result: Within the first 2 hours after administration of 4, 40, or 120 mg/kg, 50 % of the administered radioactivity was eliminated as $^{14}CO_2$. After 4 hours, 80% of the radioactivity had been expired as $^{14}CO_2$. At the end of 72 hours, 85-86% had been eliminated as $^{14}CO_2$, and 4 % and 0.6 % of the administered dose was excreted in the urine and feces, respectively. Totally, $^{14}CO_2$ accounted for 94% of the radioactivity recovered in excreta. At 400 mg/kg, slight saturation of elimination was observed.
Remarks: 1-(^{14}C)-1,4-butaneciol was administered at doses of 4, 40, 120, or 400 mg/kg to male Fischer 344 rats.
Reference: NTP working group: 1996

(f)
Type: Cumulative property
Result: The experimental results suggested an absence of any marked cumulative properties.
Remarks: Cumulative property of 1,4-butanediol was studied using guinea pigs and rats.
Reference: Knyshova: 1968

*5.11 EXPERIENCE WITH HUMAN EXPOSURE

A. Skin irritation/corrosion

Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method: Patch test
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks: Tested on 200 person
Reference: GAF: 1967

B. Skin sensitisation

Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Other
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: Unknown
Remarks: Repeated testing for 200 person
Reference: GAF: 1967

C. Other effects

(a)
Result: 15 or 30 g of 1,4-butanediol (calculated as 0.21 or 0.43 g/kg b.w., based on an assumed body weight of 70 kg) was rectally administered to 7 patients. After 10 to 20 minutes, the patients became coma after deep unconsciousness, miosis and complete areflexia and this condition continued for 1 to 16 hr. Two of them died with in 72 hours after the administration, but other five patients recovered naturally or after treatment with analeptic. Sustained disorder was not observed. Renal disorder was found in two died patients.
Remarks:
Reference: Hinrichs *et al.*: 1948

(b)
Result: Sleep is induced by intravenous administration of 30 mg/kg body weight or by infusion of 15 to 22 mg/kg/hr for about 38 to 68 hr (initial dose: 30 mg/kg body weight). Undesirable side-effects include restlessness and clonic spasms of the muscle of the extremities.
Remarks:
Reference: Toxikologische Bewertung: 1993

(c)
Result: A 44-year-old male taken into police custody for publish intoxication became agitated, lost consciousness, and vomited. Upon arrival in the ED he was unconscious with myoclonic jerking (HR: 40, RR: 8). Blood ethanol was negative. Within 3 hr he was awake, alert, and reported ingesting nine yohimbine tablets and a few sprays of "pine needle oil".
Remarks: A 3 oz opaque white pump spray bottle with a citrus smelling liquid reported to contain "pine needle oil" was analysed by DEA Western Labs to contain 1,4-butanediol.
Reference: Dyer *et al.*: 1997

(d)
Result: After one man took Thunder Nectar, he died. His wife, who also took Thunder Nectar, was unconscious for several hours but survived
Remarks: "Thunder Nectar" was a brand name of product including 1,4-butanediol.
Reference: Gugliotta: 1999

(e)
Result: A least three people had died and more than 100 had become ill after taking unregulated new products, which are listed as "party drugs" on internet sites, advertised in muscle-building magazines, and sold in health food stores as dietary supplements to aid in sleep.
Remarks: These products contain 1,4-butanediol.
According to FDA, 1,4-butanediol can cause dangerously low respiratory rates, unconscious, vomiting, seizures and death. In addition, this chemical may also increase the effects of alcohol, and is even more dangerous when consumed with other depressant drugs.
Reference: FDA talk paper: 1999

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Appendix 1

1,4-Butanediol

scenario 1

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1,000	6.3.E-07	6.3.E+03	0.4	2.9E+01	6.3.E+01
water	0	3.4.E-02	6.8.E+05	47.7	1.1E+02	6.8.E+02
soil	0	4.6.E-01	7.4.E+05	51.6	1.2E+02	
sediment		2.5.E-02	2.5.E+03	0.2	4.1E-01	5.1.E-02
		total amount	1.4.E+06			

scenario 2

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	1.9.E-10	1.9.E+00	0.0	8.7.E-03	1.9.E-02
water	1000	4.3.E-02	8.6.E+05	99.6	1.4.E+02	8.6.E+02
soil	0	1.4.E-04	2.2.E+02	0.0	3.5.E-02	
sediment		3.2.E-02	3.2.E+03	0.4	5.2.E-01	6.5.E-02
		total amount	8.6.E+05			

scenario 3

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	2.6.E-08	2.6.E+02	0.0	1.2.E+00	2.6.E+00
water	0	3.6.E-02	7.2.E+05	41.4	1.2.E+02	7.2.E+02
soil	1000	6.3.E-01	1.0.E+06	58.4	1.6.E+02	
sediment		2.7.E-02	2.7.E+03	0.2	4.3.E-01	5.4.E-02
		total amount	1.7.E+06			

scenario 4

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	600	3.8.E-07	3.8.E+03	0.3	1.8.E+01	3.8.E+01
water	300	3.7.E-02	7.4.E+05	57.3	1.2.E+02	7.4.E+02
soil	100	3.4.E-01	5.4.E+05	42.2	8.7.E+01	
sediment		2.8.E-02	2.8.E+03	0.2	4.4.E-01	5.5.E-02
		total amount	1.3.E+06			

Physico-chemical parameter

molecular weight	90.12	Measured	Temp. ^{0}C	25

melting point		20	Measured
vapor pressure [Pa]		1.9E+00	Measured
water solubility [g/m^3]		100000	Measured
log Kow		-0.5	Measured
half life [h]	in air	150	Estimated
	in water	4320	Estimated
	in soil	4320	Estimated
	in sediment	4320	Estimated

Environmental parameter

		volume	depth	area	organic	lipid content	density	residence
		[m^3]	[m]	[m^2]	carbon []	[]	[kg/m^3]	time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters m/h

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

EXTRACT FROM IRPTC LEGAL FILES

file: 17.01 LEGAL rn : 522395
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :1,4-Butanediol
cas no :110-63-4 rtecs no :EK0525000
area : DEU type : REG

subject	specification	descriptor
AQ USE	INDST	CLASS RQR

This substance is classified as moderately hazardous to water (Water Hazard Class: WHC 1). (There are 3 water hazard classes: WHC 3 = severely hazardous; WHC 2 = hazardous; WHC 1 = moderately hazardous; and the classification as "not hazardous to water"). The purpose of the classification is to identify the technical requirements of industrial plants which handle substances hazardous to water.
entry date: SEP 2001 effective date: 01JUN1999

title: Administrative Order relating to Substances Hazardous to Water (Verwaltungsvorschrift wassergefaehrdende Stoffe)
original : BUANZ*, Bundesanzeiger, 51 , 98a , 1 , 1999

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file: 17.01 LEGAL rn : 1121591
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :Butane-1,4-diol
cas no :110-63-4 rtecs no :EK0525000
area : RUS type : REG

subject	specification	descriptor
AIR	AMBI	PSL

0.1MG/M3 1X/D
entry date: SEP 1985 effective date: NOV1984

amendment: OBUAV*, ORIENTIROVOCHNYE BEZOPASNYE UROVNI VOZDEISTVIA (OBUV) ZAGRAZNIAIUSHCHIKH VESHCHESTU V ATMOSFERNOM VOZDUKHE NASEKENNYKH MEST (TENTATIVE SAFE EXPOSURE LIMITS (TSEL) OF CONTAMINANTS IN AMBIENTAIR OF RESIDENTIAL AREAS), 3165-84 , , , 1984

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file: 17.01 LEGAL rn : 1122726
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :1,4-Butanediol
cas no :110-63-4 rtecs no :EK0525000
area : RUS type : REG

subject	specification	descriptor
AQ	SURF	MAC CLASS

5.0MG/L HAZARD CLASS: II
entry date: JUL 1990 effective date: 1JAN1989

amendment: SPNPV*, SANITARNYE PRAVILA I NORMY OKHRANY POVERKHNOSTNYKH VOD OT ZAGRIAZNENIA (HEALTH REGULATION AND STANDARDS OF SURFACE WATER PROTECTION FROM CONTAMINATION), 4630-88 , , , 1988

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file: 17.01 LEGAL rn : 1302084
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :1,4-Butanediol
cas no :110-63-4 rtecs no :EK0525000
area : USA type : REG

subject	specification	descriptor
FOOD	ADDIT	RSTR
TRANS		RSTR
STORE		RSTR
PACK		RSTR

; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF SUBSTANCES USED TO PREPARE ADHESIVES WHICH MAY BE SAFELY USED AS COMPONENTS OF ARTICLES INTENDED FOR USE IN PACKAGING, TRANSPORTATION, OR HOLDING FOOD IN ACCORDANCE WITH THE FOLLOWING PRESCRIBED CONDITIONS: SUBSTA NCE MUST BE SEPARATED FROM THE FOOD BY A FUNCTIONAL BARRIER, MUST NOT EXCEED LIMITS OF GOOD MANUFACTURING PRACTICE USED WITH DRY FOODS, OR NOT EXCEED TRACE AMOUNTS AT SEAMS AND EDGE EXPOSURES WHEN USED WITH FATTY AND AQUEOUS FOODS. ALSO REGULATED BY SEA M INTEGRITY, LABELING STANDARDS, AND ANY PROVISION UNDER 21 CFR 175
entry date: NOV 1991 effective date: 1977

title: SUBSTANCES FOR USE ONLY AS COMPONENTS OF ADHESIVES
original : FEREAC, FEDERAL REGISTER, 42 , , 14534 , 1977
amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 21 , 175 , 105 , 1988

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file: 17.01 LEGAL rn : 1408526
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :1,4-Butanediol
cas no :110-63-4 rtecs no :EK0525000
area : EEC type : REG

subject	specification	descriptor
FOOD		RQR
GOODS		MXL
GOODS		PRMT

THE SUBSTANCE IS INCLUDED IN THE LIST OF MONOMERS AND OTHER STARTING SUBSTANCES, WHICH MAY CONTINUE TO BE USED FOR THE MANUFACTURE OF PLASTICS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS UNTIL 1 JANUARY 1997 PENDING A DECISION ON THEIR INCLUSION IN THE LIST OF AUTHORIZED SUBSTANCES. THE USE OF THE SUBSTANCE IS SUBJECT TO THE RESTRICTIONS SPECIFIED THEREIN. PLASTIC MATERIALS AND ARTICLES SHALL NOT TRANSFER THEIR CONSTITUENTS TO FOODSTUFFS IN QUANTITIES EXCEEDING 10MG/DM2 OF SURFACE AREA OF MATERIAL OR ARTICLE OR 60 MG/KG OF FOODSTUFFS IN THE SPECIFIED CASES. VERIFICATION OF COMPLIANCE WITH THE MIGRATION LIMITS SHALL BE CARRIED OUT IN ACCORDANCE WITH DIRECTIVES 82/711/EEC AND 85/572/EEC.
entry date: SEP 1995 effective date: 01JAN1991

title: COMMISSION DIRECTIVE OF 23 FEBRUARY 1990 RELATING TO PLASTICS MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS (90/128/EEC)
original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L75 , , 19 , 1990
amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L90 , , 26 , 1993

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file: 17.01 LEGAL rn : 1470412
!!! WARNING - not original IRPTC record - WARNING !!!
systematic name:1,4-Butanediol
common name :1,4-Butanediol
reported name :Butane-1,4-diol
cas no :110-63-4 rtecs no :EK0525000
area : EEC type : REG

subject	specification	descriptor
MANUF	INDST	CLASS
IMPRT	INDST	CLASS

The substance is included in a list of existing substances produced or imported within the Community in quantities exceeding 1000 tonnes per year. - A system of data reporting by any manufacturer who has produced or any importer who has imported the substance, as such or in a preparation, in quanities exceeding 10 tonnes per year is established.
entry date: AUG 1999 effective date: 04JUN1993

title: Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances
original : OJECFC, Official Journal of the European Communities, L84 , , 1 , 1993