FOREWORD **INTRODUCTION**

TETRAHYDROMETHYL-1,3-ISOBENZOFURANEDIONE

CAS N°: 11070-44-3

SIDS Initial Assessment Report

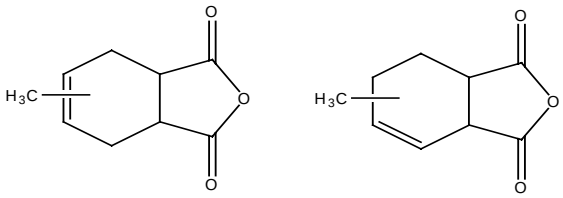
For

SIAM 15

Boston, 22-25th October 2002

1. Chemical Name:	Tetrahydromethyl-1,3-isobenzofuranedione
2. CAS Number:	11070-44-3
3. Sponsor Country:	Japan **National SIDS Contact Point in Sponsor Country**: Mr. Yasuhisa Kawamura Director Second Organisations Div. Ministry of Foreign Affairs 2-2-1 Kasumigaseki, Chiyoda-ku Tokyo 100
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	**Industry:** Mr. Katsurou Matsuo, HITACHI CHEMICAL CO., LTD. E-mail: k-matsuo@hitachi-chem.co.jp
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 15.
7. Review Process Prior to the SIAM:	The industry collected new data and prepared the updated IUCLID, and draft versions of the SIAR and SIAP. Japanese government peer-reviewed the documents, audited selected studies.
8. Quality check process:	
9. Date of Submission:	August 13, 2002
10. Date of last Update:	
11. Comments:	No testing (X) Testing ( ) ICCA Initiative work lead by HITACHI CHEMICAL CO.,LTD., Japan. (consortium member: ZEON CO., LTD.).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	11070-44-3
Chemical Name	Tetrahydromethyl-1,3-isobenzofuranedione
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

This chemical is a mixture of several chemical species as defined by the above described structure.

Human Health

There is no available information on metabolism or toxicokinetics of this substance in animals. This chemical is, nevertheless, known to metabolized to di-carboxylic acid and excreted in urine in human, when inhaled. $T_{1/2}$ for the excretion is estimated as ca. 3-6 hr.

In acute oral toxicity studies [OECD TG 401] in rats, the LD_{50} of tetrahydromethyl-1,3-isobenzofuranedione ranged from 1900 mg/kg to more than 2000 mg/kg. The major toxicity was inflammation of the forestomach, such as thickening of the forestomach mucosa, squamous hyperplasia and granulomatous inflammation.

In a primary irritation study [Federal Regulations, Title 16, Section 1500.41] with rabbits, this chemical was considered to be a moderate irritant to rabbit skin. In an eye irritation study with rabbits, this chemical is an irritant to eyes. There is no available information on sensitization in animals. Human epidemiological studies are available, showing that this chemical has sensitizing potential.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], this chemical was administered by gavage (male rats for 49 days, female rats from 14 days before mating to day 3 of lactation) at the dose levels of 30, 100 and 300 mg/kg/day. Salivation was transiently observed in males of the 300 mg/kg group after day 36 of treatment. Increased adrenal weights were observed in males of the 300 mg/kg group. Mucosal thickening of the forestomach was found in both sexes of the 300 mg/kg group. Squamous hyperplasia of the forestomach and submucosal granulomatous inflammation of the forestomach was observed in both sexes of the 300 mg/kg group. On the basis of these findings, the NOAEL of tetrahydromethyl-1,3-isobenzofuranedione was considered to be 100 mg/kg for both sexes.

In the above mentioned OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], no adverse effects were found in reproduction and development. The NOAEL for reproduction and development is considered to be 300 mg/kg/day.

Bacterial genotoxicity studies showed negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In a chromosomal aberration test conducted in cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473], structural chromosomal aberrations were not induced up to 0.30 mg/ml. Polyploidy (1.13 %) was induced at 0.30 mg/ml with a 48 hr continuous treatment without metabolic activation, and, polyploidy (1.25-1.88 %) was induced at 0.11-0.43 mg/ml in short-term treatment with an exogenous metabolic activation system. The limited evidence available indicates that this substance is not genotoxic.

Environment

The vapor pressure of tetrahydromethyl-1,3-isobenzofuranedione is estimated to be 0.0044 hPa at 25°C. When this chemical is released into water or other environment compartment it is rapidly and thoroughly hydrolyzed to the

corresponding di-carboxylic acids. It is very water soluble (>10 g/L). The acidity of the hydrolysate results in pH=4.3 at 270 mg/L. The calculated log Kow for the original anhydride form is 2.4-2.6 and for a representative hydrolysates is 0.7-1.4. These hydrolysates are not readily biodegraded. The potential of bio-accumulation of these hydrolysates estimated to be low, because experimental BCF values of related substances are low and the calculated BCF for a hydrolysate is consistently low (BCF=21.2).

The effects of tetrahydromethyl-1,3-isobenzofuranedione in aquatic organisms were studied using the hydrolysate and the values obtained were expressed as anhydride. The chemical is hydrolysed to the corresponding dibasic acids at a rate determined by the mode of mixing with water.

In acute toxicity studies to aquatic species, the toxicity to daphnids [OECD TG 202] was 130 mg/l for EC_{50} (immobility in *Daphnia magna*, 48 hr). The toxicity to fish (Medaka) [OECD TG 203] was more than 100 mg/l for LC_{50} (96 hr). The prolonged toxicity to fish (Medaka)[OECD TG 204] was more than 100 mg/l for LC_{50} (14 d).

The toxicities of tetrahydromethyl-1,3-isobenzofuranedione to algae [OECD TG 201, *Selenastrum capricornutum*] were 55 mg/l for ErC_{50} (growth rate 24-48 h) and 64 mg/l for EbC_{50} (biomass, 72 hr), 27.5 mg/l for NOEC (growth rate 24-72 h) and 27.5 mg/l for NOEC (biomass, 72 h).

The chronic toxicity to daphnids [OECD TG 202 part 2] was 9.2 mg/l for EC_{50} (reproduction, 21 d) and 0.94 mg/l for NOEC (reproduction, 21 d).

Exposure

The production volume of tetrahydromethyl-1,3-isobenzofuranedione is estimated to be 8000 t/y in Japan and 20000 t/y world-wide in 2001. The producing countries are Japan, Italy, United States of America and People's Republic of China. In Japan, this chemical is produced in closed systems. The main use is as a hardener for epoxy resins. This substance is not usually released to the environment from the production and use site, except during sampling and maintenance. This chemical is hydrolyzed to several dicarboxylic acids in water. So, the potential environmental distribution was estimated for 4-methyl-4-cyclohexene-1,2-dicarboxylic acid, one of the hydrolysation products of tetrahydromethyl-1,3-isobenzofuranedione. The fugacity model (Mackey level III) suggests that if released to air, water and soil the majority of this hydrolyzed chemical would distribute into water and soil.

Occupational exposure at production sites and processing sites may occur by the inhalation and dermal route. This substance is classified as a "sensitizing substance" in Germany (List of MAK and BAT values 2000). The Japan society for occupational health recommended 50 ug/m^3 as a limit for this substance exposure during an 8 hr work shift.

Consumer exposure of this chemical is considered to be negligible.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The sensitizing properties indicate a hazard for human health. No further work is recommended, if sufficient control measures in place to avoid significant human exposure, including prevention of accidental exposure. In situations where this is not the case, risk assessment and, if necessary, risk reduction measures are recommended.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work for the environment. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

FULL SIDS SUMMARY

CAS NO: 11070-44-3		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	< - 15 °C
2.2	Boiling Point		Unknown	290 °C at 1013 hPa
2.3	Density		JIS K 2249-1987	1.21 g/cm^3
2.4	Vapour Pressure		Unknown	0.0044 hPa at 25 °C
2.5	Partition Coefficient (Log Pow)			None
2.6 A.	Water Solubility		Unknown	Hydrolysed (Seems to be soluble at more than 10 g/L)
B.	pH			None
	pKa			None
2.12	Oxidation: Reduction Potential			None
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated	$T_{1/2}$ = 2.979 hrs
			[Calculated on 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysates of this substance)	[$T_{1/2}$ = 10.040 hrs]
3.1.2	Stability in Water			Hydrolyzed
3.2	Monitoring Data			No study
3.3	Transport and Distribution		Calculated (Level III Fugacity Model) 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysates of this substance) (local exposure)	(Release 100% to air) Air Water Soil Sediment 0.0% 31.6% 68.3% 0.2% (Release 100% to water) Air Water Soil Sediment 0.0% 99.5% 0.0% 0.5% (Release 100% to soil) Air Water Soil Sediment 0.0% 26.9% 72.9% 0.1%
3.5	Biodegradation		OECD 301C	Hydrolysates are not readily biodegradable
3.7	Bioaccumulation	Carp	OECD TG 305C	4-methyl-4-cyclohexane-1,2-dicarboxylic acid (an analogue of the hydrolysate of this substance) <0.2 at 0.5 mg/L, <2.4 at 0.05 mg/L
		Carp	OECD TG 305C	4-cyclohexene-1,2-dicarboxylic acid (an analogue of the hydrolysate of this substance) <0.2 at 2 mg/L, <2 at 0.2mg/L
			Calculated	4-methyl-4-cyclohexene-1,2-dicarboxylic acid =3.162
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50}(96 hr) > 100 mg/L :flow through
			OECD TG 204	LC_{50}(14 d) > 86 mg/L :flow through
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(48hr,Imm) = 130 mg/L :static
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50}(72hr,Bms) = 64 mg/L NOEC(72hr,Bms) = 27.5mg/L EC_{50}(24-48hr,gr) = 55 mg/L NOEC(24-72hr,gr) =27.5 mg/L :static

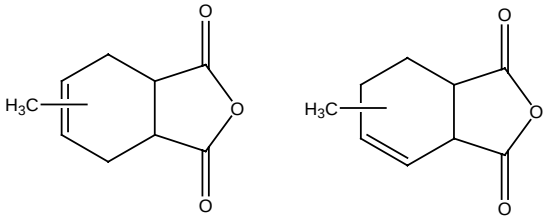
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(21d,Rep)= 9.2 mg/L NOEC(21d,Rep)= 0.94 mg/L :semi static
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat Rat	OECD TG 401 Other	LD_{50} > 2000 mg/kg LD_{50}= 1900 mg/kg
5.1.2	Acute Inhalation Toxicity			None
5.1.3	Acute Dermal Toxicity	Rabbit	Other	1.41 ml/kg
5.2.1	Skin Irritation	Rabbit	Federal Regulations Title 16 Section 1500.41	moderate
5.2.2	Eye Irritation	Rabbit	Other	Irritating
5.3	Skin Sensitisation			None
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOAEL = 100 mg/kg/day
5.5	Genetic Toxicity *in vitro*			
A.	Bacterial Test (Gene mutation)	*S.typhimurium* *E. coli*	OECD TG 471 & 472	Negative
B.	Non-Bacterial *in vitro* Test (Chromosomal aberrations)	CHL cell	OECD TG 473	Equivocal
5.6	Genetic Toxicity *in vivo* (Micronucleus Test)			None
5.7	Carcinogenicity			No data available
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL Reproductive/Developmental= 300 mg/kg/day.
5.9	Developmental Toxicity/ Teratogenicity			No teratogenicity
5.11	Experience with Human Exposure			No data available

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 11070-44-3
IUPAC Name: Tetrahydromethyl-1,3-isobenzofuranedione
Molecular Formula: $C_9H_{10}O_3$
Structural Formula:



The composition of isomer varies from product to product.

Synonyms: (Chemical Name)

1,3-Isobenzofuranedione, tetrahydromethyl

Methyltetrahydrophthalic anhydride

Tetrahydromethylphthalic anhydride

1.2 Purity/Impurities/Additives

>99% weight/weight

Impurities: Maleic acid anhydride ca. 0.02 %

Methyl tetrahydrophthalic acid ca. 0.01 %

Additives: None

1.3 Physico-Chemical properties

Table 1: Summary of physico-chemical properties

ITEMS	PROTOCOL	RESULTS
Melting Point	Unknown	<-15°C
Boiling Point	Unknown	290°C at 1013 hPa
Density	JIS K 2249-1987	1.21 g/cm3 at 25°C
Vapor Pressure	Calculated	0.0044 hPa at 25°C
Partition Coefficient (Log Pow)	Estimated	2.64 at 25°C
Water Solubility		hydrolyzed (>10g/L)
pH	Quote from Daphnia acute tox study	4.3(at 20.7-20.9°C , 320 mg/l)
pKa		No data available

JIS : Japanese Industrial Standard

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production volume of this substance was approximately 8,000 t/y in Japan and 20,000 t/y world-wide in 2001. The producing countries are Japan, Italy, United States of America and People's Republic of China. In Japan, this substance is produced in closed systems.

The main use is a hardener for epoxy resins.

This substance is not usually released to the environment from the production and use site, except during sampling and maintenance.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

It is confirmed that tetrahydromethyl-1,3-isobenzofuranedione hydrolyzes to the corresponding di-carboxylic acid in water. Therefore, this substance is considered to be hydrolyzed to the corresponding di-carboxylic acids (Fig. 1) in the environment.

These hydrolysates are considered to be stable in the water phase. The potential environmental distribution of 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (Fig. 2, one of the representative hydrolysate of tetrahydromethyl-1, 3-isobenzofuranedion) obtained from a generic fugacity model Mackey level III is shown in Table 2.

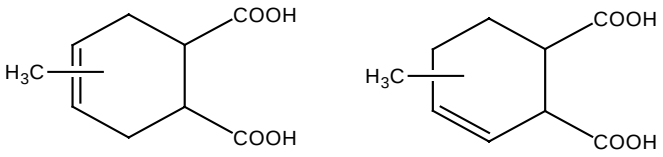


Fig. 1: Structural formula of hydrolysates of tetrahydromethyl-1, 3-isobenzofuranedione

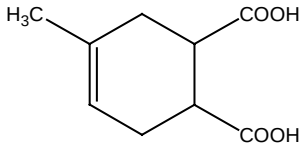


Fig. 2: Structural formula of 4-methyl-4-cyclohexene-1, 2-dicarboxylic acid

Table 2: Environmental distribution of 4-methyl-4-cyclohexene-1, 2-dicarboxylic acid using the fugacity model (Mackay level III) under three emission scenarios

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	0.0%	0.0%	0.0%
Water	31.6%	99.5%	26.9%
Soil	68.3%	0.0%	72.9%
Sediment	0.2%	0.5%	0.1%

The hydrolysates are not readily biodegradable [OECD TG 301C :0 % based on BOD and 0 % based on TOC during 28 day (MITI, Japan 1997)].

These hydrolysates are considered to have a low bioaccumulation potential, because the calculated BCF for a representative hydrolysate (4-methyl-4-cyclohexene-1,2-dicarboxylic acid) is consistently low (BCF=3.162) and the experimental BCF value of 4-methylcyclohexane-1,2-dicarboxylic acid (Fig. 3, CAS 57567-84-7, BCF value: <0.2 at 0.5mg/l, <2.4 at 0.05mg/l) and 4-cyclohexene-1,2-dicarboxylic acid (Fig. 4, CAS 88-98-2, BCF value:<0.2 at 2 mg/l, <2 at 0.2mg/l), analogues of hydrolysates of this substance, is low (MITI, Japan 1992).

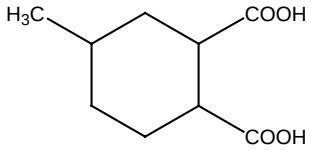


Fig. 3: Structural formula of 4-methylcyclohexane-1, 2-dicarboxylic acid

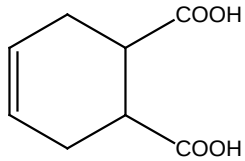


Fig. 4: Structural formula of 4-cyclohexene-1, 2-dicarboxylic acid

2.3 Human Exposure

2.3.1 Occupational Exposure

In Japan, this substance is produced in a closed system.

The occupational exposures are expected through inhalation and dermal route. Occupational exposure may occur at the production site and processing sites.

The atmospheric concentration was measured at several sites. The monitored data at a production site and several processing site are shown in Table 3 and Table 4, respectively.

Table 3: Occupational exposure levels and maximum EHE values at a production site

Occupation (Country)	Operation	Frequency Times/day	Working hr/time	Monitoring data (ug/m^3)		Maximum EHE (ug/kg/day)
				Mean	Maximum	
Production Plant (Japan)	Sampling	3.8	0.05	823	3267	11.1
	Analysis	3.0	0.02	4	5	0.01
	Drum filling	0.8	5	14	40	2.86

The atmospheric concentration was measured at a production site (Table 3; Japan Industrial Safety and Health Association 2002). The maximum atmospheric concentration in production site was 3267 ug/m^3 at sampling work.

Table 4: Occupational exposure levels at processing sites

Occupation (country)	Process	Monitoring data (ug/m^3)		Source (year)
		geometric mean	Maximum	
Processing Plant A (Japan)	Assembly 1	30.2	102	Yokota, K. et al. (1996,1997, 1998a and 1999)
	Assembly 2	63.9	421	
	Loading and hardening 1	68.4	124	
	Loading and hardening 2	65.9	278	
	Inspection	25.5	67.9	
Processing Plant B (Japan)	Assembly	4.93	14.9	
	Loading and hardening 1	61.1	107	
	Loading and hardening 2	56.8	149	
	Inspection	5.49	22.4	
Processing Plant (Sweden)	hand swabbing epoxy resin	100 *	-	Nielsen, J et al. (1989)
	handling epoxy resin	100,15,14 and 10 *	380	Welinder, H. et al. (1990)
	handling epoxy resin and curing	20-150 and 5-20 *	-	Nielsen, J. et al. (1992)
		20-100 *	-	Nielsen, J. et al. (1994)
	handling epoxy resin	<0.5-26.2, 2.1-57.9,	37.2-58.5 #	Drexler, H. et al. (2000)

*:Time weighted average

#:monitoring data in three plants

A maximum exposure at the production site is estimated as follows: If a certain worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) is assigned to sampling, analysis and drum filling of this substance without protection, the combined maximum estimated human exposure (EHE combined) is calculated as 13.97 ug/kg/day in the worst case. Workers recognize the fact that this substance has irritating activity to skin and they are recommended to wear protective equipment (mask, goggle and glove) during work, so dermal exposure was negligible.

This substance is mainly used as epoxy resin hardener, so occupational exposure may also occur during coating and curing processes. The atmospheric concentration was measured at some processing sites (Table 4). The maximum atmospheric concentration at a processing site was 421 ug/m^3 (Yokota, K. et al. 1998a).

A maximum exposure at a processing site is estimated as follows: If a single worker [exposure level: 421 ug/m^3 (maximum concentration at assembly 2 process in plant A), body weight; 70 kg, respiratory volume 1.25 m^3/hr, working time: 8 hr] is assigned to implement this operation without protection, the highest daily intake is calculated as 60.1 ug/kg/day.

The Japan Society for Occupational Health recommended 50 ug/m^3 (TWA) as a limit for exposure to this substance during an 8 hr work shift. This limit value has been decided based on the relation between exposure level and specific IgE.

2.3.2 Consumer Exposure

This substance is used as chemical intermediate for epoxy resins. After polymerization into resins, the release of this substance is considered to be low. Thus it can be considered that exposure for consumers is negligible.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

There is no available information on toxicokinetics in experimental animals.

Studies in Humans

In humans, this substance is taken up through the respiratory way by inhalation and is metabolized to the corresponding di-carboxylic acids and excreted in urine. The half-times of the urine concentration of these di-carboxylic acids were 3-6 hr (Lindh, C. H. and Jonsson, B. A. G. 1994). There is a related study performed in hexahydrophthalic anhydride (HHPA: an analogue of tetrahydromethyl-1, 3-isobenzofuranedione). The respiratory uptake of the inhaled HHPA was almost complete. Rapid increases in plasma and urinary levels of hexahydrophthalic acid (HHA acid) were seen. During the first 4 hr after the end of exposure, the half-life of HHA acid in plasma was about 2 hr and a corresponding decay was seen in urine (Jonsson, B. A. G. 1993). These results suggested that excretion of tetrahydromethyl-1, 3-isobenzofuranedione from humans is considered to be rapid.

3.1.2 Acute Toxicity

Studies in Animals

Oral

Among the several acute toxicity studies summarized in table 5, there are two key studies. The first oral rat study (MHW, Japan, 1997a) was identified as the best quality and the key study because it was conducted in line with OECD TG 401 and described in detail. In this study, this substance was studied for oral toxicity in rats in a single dose toxicity test at doses of 0, 500, 1000 and 2000 mg/kg for both sexes. No deaths occurred of either males or females. Clinical signs of hypoactivity, bradypnea and prone position were observed in males and females of the 2000 mg/kg group on the day of administration. Decrease of body weights was observed in males of the 2000 mg/kg group and suppression of body weight gain was observed in females of the 2000 mg/kg group on the day of administration. At necropsy, thickening of the forestomach mucosal was observed in males and females of the 1000 and 2000 mg/kg groups. Adhesion of forestomach and liver was noted in one female of the 2000 mg/kg group. Histopathologically, squamous hyperplasia and granulomatous inflammation in submucosal of the forestomach were observed in the 1000 and 2000 mg/kg groups. A foreign body granuloma in the adhesion area was also noted in the female of the 2000 mg/kg group. As the result, the LD_{50} value is >2000 mg/kg.

The second oral rat study (Huntingdon Research Center, 1980a) was reliable, but it was not conducted in line with the OECD guideline and there was no histopathological information. In this study the LD_{50} value was 1900 mg/kg.

In summary, based on the two studies described above, oral LD_{50} values were >2000 mg/kg and 1900 mg/kg for rats. The major toxicity was squamous hyperplasia of the forestomach.

Intraperitoneal or dermal studies are not discussed in detail because the details were not described.

Table 5: Acute toxicity of tetrahydromethyl-1, 3-isobenzofuranedione

Route	Animals	Values(Sex)	Type	GLP	References
Oral					
	Rat	>2000 mg/kg(both sex)	LD_{50}	Y	MHW Japan (1997a)
	Rat	1900mg/kg(both sex)	LD_{50}	Y	Huntingdon Research Center (1980a)
	Rat	2102mg/kg(both sex)	LD_{50}	N	Hitachi Chemical (1969)
	Mouse	1707 mg/kg(male)	LD_{50}	N	Hitachi Chemical (1969)
	Rat	2140 mg/kg(not cited)	LD_{50}	unknown	Lonza SpA (2000)
	Rat	2.14 ml/kg*(not cited)	LD_{50}	unknown	H. F. Smyth et.al. (1969)#
Intra peritoneal					
	Rat	255 mg/kg(male)	LD_{50}	N	Hitachi Chemical (1969)
	Mouse	222 mg/kg(male)	LD_{50}	N	Hitachi Chemical (1969)
Dermal					
	Rabbit	1.41 ml/kg*(not cited)	LD_{50}	unknown	H. F. Smyth et.al. (1969)#
	Rat	>2000 mg/kg*(not cited)	LD_{50}	Y	Lonza SpA (2000) $

*: Test substance was methyl-4-cyclohenene-1,2-dicarboxylic anhydride (CAS 26590-20-5)

#: Review article

$: Secondary information

Studies in Humans

This substance (TWA of this substance ca. 20-150 ug/m^3) caused eye and nasal symptoms such as pain of eyes, pain of pharynx, sneeze, nose secretion, nose blockage, cough and asthma. In workers exposed to this chemical, the specific IgE level was high and closely related to the symptoms. Therefore, this chemical caused allergic responses mediated by IgE (Nielsen, J. et al. 1992, Yokota, K. et al. 1998, Yokota, K. et al. 1999).

This substance is classified as “sensitizing” (List of MAK and BAT values 2000, Guide to Occupational Exposure values 2002).

Conclusion

The major toxicity was mucosal irritation caused by the acidity of this substance.

Oral LD_{50}: Male, >2000 mg/kg; female, >2000 mg/kg

3.1.3 Irritation

Skin Irritation

Two reports are available.
The first study is performed by Huntington Research Center (1980b). The primary irritation index [Code of Federal regulations. Title 16. Section 1500.41] of this substance was calculated to be 3.5, so this substance is considered to be a moderate irritant to rabbit skin.
The second report is a review article (Smyth, H. F. et al. 1969). A score of 1 on irritation on uncovered rabbits belly is reported without any further details.

Eye Irritation

Two reports are available.

The first study is performed by Hitachi Chemical (1969). Cloudy cornea and opaque eyeball were observed one minute after administration of this substance to rabbit's eyes (0.1ml/eye). At 24h, congested iris was observed. On the 10th day recovery to half eye was observed, reflection to light had normalized and the congestion was extinguished.

The second report is a review article (Smyth, H. F. et al.1969). A score of 9 on coronal injury in rabbits eye is reported without any further details.

Conclusion

Based on these observations, this substance is considered to be moderately irritant to rabbit skin and this substance is irritant to rabbit eye.

3.1.4 Sensitisation

Studies in Animals

There is no available information on animals.

Studies in Humans

Respiratory Tract

Several occupational sensitization cases by inhalation at processing sites were reported. Respiratory sensitization by this substance mediated by IgE have been reported (Nielsen, J. et al. 1992, Yokota, K. et al. 1998, Yokota, K. et al. 1999). This substance was classified as "sensitizing" (List of MAK and BAT values 2000, Guide to Occupational Exposure values 2002), but ACGIH TLV, OSHA PEL and NIOSH REL is not decided. The Japan society for occupational health has recommended 50 ug/m^3 as a limit for exposure to this substance during an 8 hr work shift.

3.1.5 Repeated Dose Toxicity

Only one oral toxicity study was performed in SD (Crj : CD) rats by an OECD combined repeat dose and reproductive/ developmental toxicity screening test (MHW, Japan 1977b) [OECD TG 422]. Therefore it was identified as a key study.

Tetrahydromethyl-1,3-isobenzofuranedione was administered by gavage at doses of 0, 30, 100 and 300 mg/kg/day for 49 days in males and from 14 days before mating to day 3 of lactation in females. All animals survived in all treated groups, except three animals died by accident (one female at 30 mg/kg, one male at 300 mg/kg and one female at 300 mg/kg). Salivation was transiently observed in males of the 300 mg/kg group at days 36-49. Histopathological examination revealed squamous hyperplasia of the forestomach in both sexes of the 300 mg/kg group, epithelial vascular change, edema and cellular inflammation of the forestomach in males of the 300 mg/kg group, and erosion of the forestomach in females of the 300 mg/kg group. There were no adverse effects on body weight and food consumption. There were no alterations related to tetrahydromethyl-1, 3-isobenzofuranedione on hematological examination. Decreased total cholesterol and BUN and increased triglyceride were observed in males of the 300 mg/kg. As a gross finding, mucosal thickening of the forestomach was found in both sexes of the 300 mg/kg group. Increased adrenal weights were observed in males of the 300 mg/kg group.

Conclusion

The major toxicity was inflammation of stomach mucosa. On the basis of this study, the NOAEL is considered to be 100 mg/kg/day for both sexes.

3.1.6 Mutagenicity

A bacterial study and a non-bacterial in vitro study were performed. The summary of the results is shown in Table 6.

Table 6: Genotoxicity studies of tetrahydromethyl-1,3-isobenzofuranedione

Type of test	Test system	Dose	MA*	Result	Reference
Bacterial test					
Ames test (reverse mutation)	*S.typhimurium* (strains TA98, TA100, TA1535, TA1537) *E.coliWP2uvrA* OECD TG 471 & 472	Up to 5 mg/plate	with	Negative	MHW, Japan (1997c)
		Up to 2 mg/plate	without	Negative	
Non-bacterial invitro test					
Chromosomal aberration test	CHL/IU cells OECD TG 473	Up to 0.43 mg/plate	with	Negative (clastogenicity) Equivocal (Polyploidy)	MHW, Japan (1997d)
		Up to 0.3 mg/plate	without	Negative (clastogenicity) Equivocal (Polyploidy)	

MA*:metabolic activation

Bacterial test

Only one report was reviewed (MHW, Japan 1997c). A reverse gene mutation assay was conducted in line with Guidance for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guidelines 471 and 472, using the pre-incubation method. Therefore it was identified as a key study.

Tetrahydromethyl-1, 3-isobenzofuranedione was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvr*A. at concentrations up to 5 mg/plate or 2 mg/plate, with or without an exogenous metabolic activation system, respectively.

In vitro Studies

Non-Bacterial *in vitro* test

Only one report was reviewed (MHW, Japan, 1997d). A chromosomal aberration test in line with Guidance for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guideline 473 was conducted using cultured Chinese hamster lung (CHL/IU) cells. Therefore it was identified as a key study.

Structural chromosomal aberrations were not induced up to 0.30 mg/ml (24 and 48hr continuous treatment without S9). Polyploidy (1.13 %) was increased at 0.30 mg/ml with 48 hr continuous

treatment without metabolic activation. Furthermore, polyploidy (1.25-1.88 %) was statistically increased at 0.11-0.43 mg/ml (all concentrations) with short-term treatment with an exogenous metabolic activation system.

The background level of polyploidy in this laboratory was 0-0.5 % (48 hr continuous treatment without S9) and 0-0.75 % (short-term treatment with S9 mix). Based on these results, genotoxicity of this chemical was equivocal, and toxicological and biological significance were considered to be negligible.

In vivo Studies

There were no available data on genotoxicity *in vivo.*

Conclusion

This substance is not genotoxic with and without an exogenous metabolic activation system in bacterial and mammalian cells.

3.1.7 Toxicity for Reproduction

Studies in Animals

Only one report was available and reviewed (MHW, Japan, 1977b). The reproductive/ developmental toxicity-screening test by gavage was conducted in line with OECD Test Guideline 422. Therefore it was identified as a key study.

In this study, this substance was given at 0 (vehicle; corn oil), 30, 100 and 300 mg/kg/day to male rats for 49 days, and to female rats from 14 days before mating to day 3 of lactation. The details of this study are as follows.

Effects on Fertility

Increase in stillborn (5.06-6.76 %) and decrease birth index (84.27-88.4 %) were observed in the 30, 100 and 300 mg/kg group, but these results were within the range of background level (stillborn 0-14.84%, birth index 80.98-96.61%). There were no adverse effects on the estrous cycle, numbers of corpora lutea and implantations, copulation index or fertility indices

Developmental Toxicity

Total litter loss in two dams of the 100 mg/kg group was observed, but not observed in the 300 mg/kg group. During the delivery and lactation period, there were no effects related to tetrahydromethyl-1,3-isobenzofuranedione in terms of gestational days, litter size and live newborns, gestation index, stillborn index, birth index, sex ratio, body weight of offspring at birth and day 4 after birth, or viability index on day 4. No external anomalies were apparent.

Studies in Humans

There is no available information on humans.

Conclusion

Increase in stillborns, decrease of birth index and total litter loss in two dams was observed. Those results were within the range of background level and there is no dose-response relationship. Therefore, the NOAEL is considered to be 300 mg/kg/day for reproductive performance of parents and for development of offspring.

3.2 Initial Assessment for Human Health

There is no available information on metabolism or toxicokinetics of this substance in animals. This chemical is, nevertheless, known to metabolized to di-carboxylic acid and excreted in urine in human, when inhaled. $T_{1/2}$ for the excretion is estimated as ca. 3-6 hr.

In acute oral toxicity studies [OECD TG 401] in rats, the LD_{50} of tetrahydromethyl-1,3-isobenzofuranedione ranged from 1900 mg/kg to more than 2000 mg/kg. The major toxicity was inflammation of the forestomach, such as thickening of the forestomach mucosa, squamous hyperplasia and granulomatous inflammation.

In a primary irritation study [Federal Regulations, Title 16, Section 1500.41] with rabbits, this chemical was considered to be a moderate irritant to rabbit skin. In an eye irritation study with rabbits, this chemical is an irritant to eyes. There is no available information on sensitization in animals. Human epidemiological studies are available, showing that this chemical has sensitizing potential.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], this chemical was administered by gavage (male rats for 49 days, female rats from 14 days before mating to day 3 of lactation) at the dose levels of 30, 100 and 300 mg/kg/day. Salivation was transiently observed in males of the 300 mg/kg group after day 36 of treatment. Increased adrenal weights were observed in males of the 300 mg/kg group. Mucosal thickening of the forestomach was found in both sexes of the 300 mg/kg group. Squamous hyperplasia of the forestomach and submucosal granulomatous inflammation of the forestomach was observed in both sexes of the 300 mg/kg group. On the basis of these findings, the NOAEL of tetrahydromethyl-1,3-isobenzofuranedione was considered to be 100 mg/kg for both sexes.

In the above mentioned OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], no adverse effects were found in reproduction and development. The NOAEL for reproduction and development is considered to be 300 mg/kg/day.

Bacterial genotoxicity studies showed negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In a chromosomal aberration test conducted in cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473], structural chromosomal aberrations were not induced up to 0.30 mg/ml. Polyploidy (1.13 %) was induced at 0.30 mg/ml with a 48 hr continuous treatment without metabolic activation, and, polyploidy (1.25-1.88 %) was induced at 0.11-0.43 mg/ml in short-term treatment with an exogenous metabolic activation system. The limited evidence available indicates that this substance is not genotoxic.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

This substance hydrolyzes to di-carboxylic acid(s) in water. So, the effects on aquatic organisms mainly reflect the toxicity of the hydrolysis products of this substance.

This substance was dissolved in dechlorinated tap water and stirred more than 60 min. By this procedure, di-carboxylic acid(s) were obtained. The concentration was expressed as anhydride weight/ volume base.

This substance has been tested in a limited number of aquatic species. Results are summarized in Table 7.

Table 7: Aquatic toxicity of tetrahydromethyl-1, 3-isobenzofuranedione

Organism	Test method	Result (mg/l)	Reference
Aquatic plants			
Green algae (*Selenastrum capricornutum*) ATCC 22662	OECD TG 201 72 hr (cl, s)	EC_{50}(72 hr, bms) = 64(mc) EC_{50}(24-48 hr, gr) = 55(mc) NOEC(72 hr, bms) = 27.5(mc) NOEC(24-72 hr, gr) = 27.5(mc)	MOE, Japan (1997a)
Invertebrates			
Water flea (*Daphnia magna*)	OECD TG 202 24, 48 hr (op, s)	EC_{50}(24 hr, imm) = 180(mc) EC_{50}(48 hr, imm) = 130(mc)	MOE, Japan (1997b)
	OECD TG 202 21 d (op, ss)	LC_{50}(21 d)>110(mc) EC_{50}(21 d, rep)=9.2(mc) NOEC(21 d, rep)=0.94(mc) LOEC(21 d, rep)=3.5(mc)	MOE, Japan (1997c)
Fish			
Medaka (*Oryzias latipes*)	OECD TG 203 96 hr (op, f)	LC_{50}(96 hr)>100(nc*)	MOE, Japan (1997d)
	OECD TG 204 14 d (op, f)	LC_{50}(14 d)>86(mc)	MOE, Japan (1997e)

cl: closed system; op: open system; f: flow through; s: static; ss: semi-static

nc: nominal concentration(actual concentration measured, and greater than 80 % of the nominal)*

mc: measured concentration; bms: biomass; gr: growth rate;

imm: immobility; rep: reproduction

In the algae growth inhibition test [OECD TG201], an EC_{50} (72 hr) of 55 mg/l (*Selenastrum capricornutum*, growth rate 24-48hr) and 64 mg/l (biomass, 72hr) were reported and the NOEC value determined was 27.5 mg/l (growth rate, 24-48 hr and biomass, 72hr). In the water flea test, the acute EC_{50} (48 hr) value for immobility to *Daphnia magna* [OECD TG 202 part 2] was 130 mg/l and the EC_{50} (21 d, reproduction) and NOEC (21 d, reproduction) from a chronic test [OECD TG 202] were 9.2 mg/l and 0.94 mg/l, respectively. It is suggested that a part of the toxicity to green algae and water fleas is due acidity.

The LC_{50} value for acute toxicity and prolonged toxicity to fish (Medaka) were reported as greater than 100 mg/l [OECD TG 203] (96 hr) and greater than 100 mg/l [OECD TG 204](14 d).

There is no available information on the toxicity to sediment dwelling organisms.

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

The vapor pressure of tetrahydromethyl-1,3-isobenzofuranedione is estimated to be 0.0044 hPa at 25°C. When this chemical is released into water or other environment compartment it is rapidly and thoroughly hydrolyzed to the corresponding di-carboxylic acids. It is very water soluble (>10 g/L). The acidity of the hydrolysate results in pH=4.3 at 270 mg/L. The calculated log Kow for the original anhydride form is 2.4-2.6 and for a representative hydrolysates is 0.7-1.4. These hydrolysates are not readily biodegraded. The potential of bio-accumulation of these hydrolysates estimated to be low, because experimental BCF values of related substances are low and the calculated BCF for a hydrolysate is consistently low (BCF=21.2).

The effects of tetrahydromethyl-1,3-isobenzofuranedione in aquatic organisms were studied using the hydrolysate and the values obtained were expressed as anhydride. The chemical is hydrolysed to the corresponding dibasic acids at a rate determined by the mode of mixing with water.

In acute toxicity studies to aquatic species, the toxicity to daphnids [OECD TG 202] was 130 mg/l for EC_{50} (immobility in *Daphnia magna*, 48 hr). The toxicity to fish (Medaka) [OECD TG 203] was more than 100 mg/l for LC_{50} (96 hr). The prolonged toxicity to fish (Medaka)[OECD TG 204] was more than 100 mg/l for LC_{50} (14 d).

The toxicities of tetrahydromethyl-1,3-isobenzofuranedione to algae [OECD TG 201, *Selenastrum capricornutum*] were 55 mg/l for ErC_{50} (growth rate 24-48 h) and 64 mg/l for EbC_{50} (biomass, 72 hr), 27.5 mg/l for NOEC (growth rate 24-72 h) and 27.5 mg/l for NOEC (biomass, 72 h).

The chronic toxicity to daphnids [OECD TG 202 part 2] was 9.2 mg/l for EC_{50} (reproduction, 21 d) and 0.94 mg/l for NOEC (reproduction, 21 d).

5 RECOMMENDATIONS

The chemical is currently of low priority for further work

Human Health: The sensitizing properties indicate a hazard for human health. No further work is recommended, if sufficient control measures in place to avoid significant human exposure, including prevention of accidental exposure. In situations where this is not the case, risk assessment and, if necessary, risk reduction measures are recommended.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work for the environment. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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I U C L I D

D a t a S e t

Existing Chemical	ID: 11070-44-3
CAS No.	11070-44-3
EINECS Name	tetrahydromethylphthalic anhydride
EC No.	234-290-7
Molecular Formula	C9H10O3
Producer Related Part	
Company:	Hitachi Chemical Co., Ltd
Creation date:	07-MAY-2002
Substance Related Part	
Company:	Hitachi Chemical Co., Ltd
Creation date:	07-MAY-2002
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 15 (22-25 October 2002)
Printing date:	13-MAY-2004
Revision date:	
Date of last Update:	13-MAY-2004
Number of Pages:	57
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

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26-AUG-2002

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26-AUG-2002

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

IUPAC Name: Tetrahydromethyl-1,3-isobenzofuranedione
Mol. Formula: C9H10O3
Mol. Weight: 166.18

Remark: This substance is mixture of isomers. The composition of isomers is varies from product to product.

29-JAN-2003

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: > 99 - % w/w
Colour: Clear

Odour: Faint odor

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
07-MAY-2002

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,3-Isobenzofuranedion, tetrahydromethyl

Flag: Critical study for SIDS endpoint
02-AUG-2002

HN-200

Flag: Critical study for SIDS endpoint
06-JAN-2003

Methyltetrahydrophthalic anhydride

Flag: Critical study for SIDS endpoint
06-JAN-2003

MTHPA

Flag: Critical study for SIDS endpoint
06-JAN-2003

Quinhard 200

Flag: Critical study for SIDS endpoint
06-JAN-2003

Tetrahydromethylphthalic anhydride

Flag: Critical study for SIDS endpoint
06-JAN-2003

1.3 Impurities

Purity type: typical for marketed substance
CAS-No: 108-31-6
EC-No: 203-571-6
EINECS-Name: maleic anhydride
Mol. Formula: C4H2O3
Contents: ca. .02 - % w/w

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
07-MAY-2002

Purity type: typical for marketed substance
CAS-No: 27636-53-7
EINECS-Name: Methyl tetrahydrophtalic acid
Mol. Formula: C9H12O4
Contents: ca. .01 - % w/w

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
13-JUN-2002

1.4 Additives

1.5 Total Quantity

Quantity: ca. 20000 tonnes produced in 2001

Remark: produced ca. 8000 tonns/year in Japan.
07-AUG-2002

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (Xi) irritating
R-Phrases: (36/37/38) Irritating to eyes, respiratory system and skin
S-Phrases: (24/25) Avoid contact with skin and eyes
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(37/39) Wear suitable gloves and eye/face protection

02-AUG-2002

Labelling: as in Directive 67/548/EEC
Symbols: (Xn) harmful
Nota: (C) Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers
(D) Certain substances which are susceptible in spontaneous polymerisation or decomposition are generally placed on the market in a stabilized form. It is in this form that they are listed in Annex 1 to this Directive
Specific limits: no data
R-Phrases: (41) Risk of serious damage to eyes
(42/43) May cause sensitization by inhalation and skin contact
S-Phrases: (2) Keep out of reach of children
(22) Do not breathe dust
(24) Avoid contact with skin
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(37/39) Wear suitable gloves and eye/face protection

10-MAY-2002

10-MAY-2002

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: irritating
R-Phrases: (41) Risk of serious damage to eyes

10-MAY-2002

Classified: as in Directive 67/548/EEC
R-Phrases: (42/43) May cause sensitization by inhalation and skin contact

10-MAY-2002

1.6.3 Packaging

1.7 Use Pattern

Type: industrial
Category: Chemical industry: used in synthesis

Reliability: (2) valid with restrictions
07-MAY-2002

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: other:Recomendation of Occupational exposure limits
Limit value: .05 mg/m3

Source: Japan Society for Occupational Health
06-AUG-2002 (13)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Human: exposure by production
Exposure to the: Substance

Result: At a production site: Exposure is possible when sampling, analyzing and drum filling. The exposure time is estimated 0.19 hr, 0.05 hr and 4 hr for sampling, analyzing and drum filling, respectively. A maximum exposure production site is estimated as follows: If a certain worker (body weight; 70 kg. respiratory volume; 1.25 m3/hr) is assigned to sampling, analysis and drum filling of this substance without protection, the combined maximum estimated human exposure (EHE combined) is calculated as 13.97 ug/kg/day in the worst case. The work place is provided with an air ventilator. Workrs recognize the fact that this substance has irritating activity to skin and they are recommended to wear protective equipment (musk, rubber gloves and goggles) during work, so dermal exposure was negligible. Spill is collected and incinerated.
At processing site: This chemical is used as an epoxy resin hardener. Exposure is caused at coating and curing process. Potential exposure is controlled by the use of ventilation. A maximum exposure at processing site is estimated as follows: If a single worker [exposure level: 421 ug/m3 (maximum concentration at assembly process in Japanease plant), body weight; 70 kg,respiratory volume 1.25 m3/hr, working time; 8 hr] is assigned to implement this operation without protection, the highest daily intake is calculated as 60.1 ug/kg/day the worst case.

Reliability: (2) valid with restrictions
16-JUL-2002

1.11 Additional Remarks

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = -38 degree C
Decomposition: no at degree C
Sublimation: no

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
06-JAN-2003

Value: < -15 degree C
Decomposition: no at degree C
Sublimation: no

Method: other:Not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
07-MAY-2002 (9)

2.2 Boiling Point

Value: = 120 degree C at 4 hPa
Decomposition: yes

Method: other: Not stated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
07-MAY-2002 (9)

Value: = 150 degree C at 13.5 hPa
Decomposition: no

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
30-JAN-2003

Value: = 210 degree C at 136 hPa
Decomposition: no

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
30-JAN-2003

Value: = 290 degree C at 1013 hPa
Decomposition: no

Method: other:Not stated
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
07-MAY-2002 (9)

2.3 Density

Type: density
Value: = 1.19 g/cm³ at 25 degree C

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
06-JAN-2003

Type: density
Value: = 1.21 at 25 degree C

Method: other: JIS K 2249-1987
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
07-MAY-2002 (9)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .0044 hPa at 25 degree C
Decomposition: no

Method: other (calculated): antoine
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
02-JUL-2002

Value: = 13.5 hPa at 150 degree C

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
30-JAN-2003

Value: = 136 hPa at 210 degree C

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
30-JAN-2003

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = .7 - 1.4 at 25 degree C

Method: other (calculated)
Year: 2002
GLP: no

Method: using KOWWIN v1.66
Test substance: hydrolysates of this substance.
06-JAN-2003

Partition Coeff.: octanol-water
log Pow: = 2.64 at 25 degree C

Method: other (calculated)
Year: 2002
GLP: no

Method: using KOWWIN v1.66
Reliability: (2) valid with restrictions
06-JAN-2003

2.6.1 Solubility in different media

Solubility in: Water
Value: = 176.4 g/l at 20 degree C

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
06-JAN-2003

Solubility in: Water
Value: > 10 at 25 degree C

Result: This substance was solbule in water (>10g/L). It is considered that this substance was hydrolyzed in water because di-carboxylic structure was confirmed by IR spectrum.
Source: Hitachi Chemical Co.,Ltd.
Test substance: as presdribed by 1.1-1.4
Reliability: (2) valid with restrictions
06-JAN-2003

2.6.2 Surface Tension

2.7 Flash Point

Value: = 148 degree C
Type: open cup

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable

30-JAN-2003

Value: = 157 degree C
Type: open cup

Method: other: Cleveland open type
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
07-MAY-2002

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
Light source: Sun light
Conc. of subst.: at 25 degree C
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1.5 molecule/cm³

Method: other (calculated)
Year: 2002
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Caluculated by using AOPWIN (v1.90)
Result: Rate constant: 43.0843X10 E-12cm3/molecule-sec
Photodegradation half-life is estimated as 2.979 hr
Source: Hitachi Chemical Co., Ltd.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
30-JAN-2003

Type: air
Light source: Sun light
Conc. of subst.: at 25 degree C
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1.5 molecule/cm³

Method: other (calculated):
Year: 2002
GLP: no
Test substance: other TS

Method: Caluculated by using AOPWIN (v1.90)
Result: Rate constant: 12.784X10 E-12cm3/molecule-sec
Rate constant: 43.0843X10 E-12cm3/molecule-sec
Photodegradation half-life is estimated as 10.04 hr
Source: Hitachi Chemical Co., Ltd.
Test substance: 4-methyl 4-cyclohexane-1,2-dicarboxylic acid (Representative hydrolysate of tetrahydromethyl-1,3-isobenzofuranedione).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
30-JAN-2003

3.1.2 Stability in Water

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level III
Year: 2001

Result: Tetrahydromethyl-1,3-isobenzofuranedione is considered to be hydrolyzed to 3-methyl-4(or 3)-cyclohexene-1,2-dicarboxylic acid and/or 4-cyclohexene-1,2-dicarboxylic acid in environment. So, the potential environmental distribution of 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysate of tetrahydromethyl-1,3-isobenzofuranedion) obtained from a generic level III fugacity model is shown below

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0 %	0.0 %	0.0 %
Water	31.6 %	99.5 %	26.9 %
Soil	68.3 %	0.0 %	72.9 %
Sediment	0.2 %	0.5 %	0.1 %

Attached doc.: 11070443_APPENDIX1.doc
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
13-MAY-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 0 % after 28 day(s)
Result: under test conditions no biodegradation observed
Control Subst.: Aniline
Kinetic: 7 day(s) = 66 %
14 day(s) = 79 %
Deg. product: yes

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Test condition: Water temparatyre : 24-26 ‹C
Number of replicate : 3
Reliability: (1) valid without restriction
carried out by Chemicals Inspection & Testing Institute, Japan
Flag: Critical study for SIDS endpoint
30-JAN-2003

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 28 day(s) at 25 degree C
Concentration: .5 mg/l
BCF: < .2
Elimination: no data

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
GLP: yes
Test substance: other TS

Test substance: 4-methylcyclohexane-1,2-dicarboxylic acid. CAS No.57567-84-7
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
19-APR-2004 (1)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 28 day(s) at 25 degree C
Concentration: 2 mg/l
BCF: < .2
Elimination: no data

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
GLP: yes
Test substance: other TS

Test substance: 4-cyclohexene-1,2-dicarboxylic acid. CAS No. 88-98-2
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-JAN-2003 (2)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 28 day(s)
Concentration: .2 mg/l
BCF: < 2
Elimination: no data

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
GLP: yes
Test substance: other TS

Test substance: 4-cyclohexene-1,2-dicarboxylic acid. CAS No. 88-98-2
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-JAN-2003 (2)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 28 day(s) at 25 degree C
Concentration: .005 mg/l
BCF: < 2.4
Elimination: no data

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
GLP: yes
Test substance: other TS

Test substance: 4-methylcyclohexane-1,2-dicarboxylic acid. CAS No.57567-84-7
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-JAN-2003 (1)

BCF: = 3.16
Elimination: no data

Method: other
Year: 2002
GLP: no
Test substance: other TS

Method: Caluculated by using BCFWIN (v2.14)
Source: Hitachi Chemical Co., Ltd.
Test substance: 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysate of tetrahydromethyl-1,3-isobenzofurandion)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
31-JAN-2003

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC0: = 100 - measured/nominal
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 1997
GLP: yes
Test substance: other TS: hydrolyzed substance of prescribed by 1.1-1.4

Method: Statistical methods: Not used (because this study was limit test)
Result: - Nominal concentrations:

Nominal concentration (mg/l)	Measured concentration(mg/l) (percentage of nominal) 0-hr	24-hr	Mean*
Control	<5	<5	-
100	84 (84)	90 (90)	86

* The values are expressed as arithmetic mean.
Nominal/measured concentration:
0 hr;84.0 %, 24 hr(water renewal);90.0 %

-Water Temperature: 23.7-24.0 degrees C
-Water Chemistry in test:
DO = 7.5-7.8 mg/l(>=60 % Oxygen saturation level)
-pH 6.3-7.9
pH values during a 96 hr flow-through exposure of Medaka (Oryzias latipes) to hydrolysates of tetrahydromethyl-1,3-isobenzofurandione:

Measured concentration (mg/l)	pH 0-hr	24-hr	48-hr	72-hr	96-hr
Control	7.9	7.9	7.9	7.9	7.9
100	6.3	6.4	6.4	6.4	6.3

-Cumulative mortality:

Measured concentration (mg/l)	Cumulative number of dead fish (percentage mortality) 24-hr	48-hr	72-hr	96-hr
Control	0(0)	0(0)	0(0)	0(0)
100	0(0)	0(0)	0(0)	0(0)

- LC50 >100 mg/l
LC0 =100 mg/l based on nominal concentration
-Other effects :
Toxic symptoms : Toxic symptoms was not observed
Source: MOE Japan

Test condition: -Test Organisms:
a)Size (length and weight):
length = 20-22 mm; weight =0.15-0.19 g
b)Supplier/Source: obtained from commercial hatchery
(nango suisan center, shiga-pref. Japan)
-Sensitivity:96 hr LC50 of
reference substance (CuSO4 5H2O) = 3.6 mg/l
-Test design : A limit test was conducted with a
100 mg/l of test substance and a dilution water control.
-Test Condition:
a)Dilution Water Source: dechlorinated tap water
b)Dilution Water Chemistry:
hardness = 62 mg/l as CaCO3
pH = 7.9, chlorine concentration <0.01 mg/l
c)Exposure Vessel Type:
5.0 l test solution in glass vessel
d)Nominal Concentration(as mg/l): 0 and 100
(Nominal concentration << water solubility(>1000 mg/l))
e)Vehicle/Solvent and Concentrations:
Solvent;Not used
f) Stock Solutions Preparations and Stability:
Tetrahydromethyl-1,3-isobenzofuranedione was added in
dechlorinated tap water (1000 mg/l) and stirred more than
60 min by magnetic stirrer. The test solution
was supplied continuously by mixing the working solution
and the dilution water with the help of a mechanically
operated quantitative water-pump.
g)Number of Replicates: 1
h)Fish per Replicates: 10
i)Flow-through Rate : 35 ml/min
j)Water temperature 23-25 degrees C
(measured 23.7-24.0 degrees C)
k)Intensity of Irradiation: room light
l)Photoperiod: 16h:8h light-dark cycle
-Analytical Method: HPLC
-Statistical Method:
a)Data Analysis: Not described
b)Method of Calculating Mean Measured Concentrations :
Toxicity was estimated based on nominal concentrations
because the analytical measurement showed test
concentration were apperrently within 20 % difference
to nominal.
Reliability: (1) valid without restriction
carried out by Sumika Technoservice Co.
Flag: Critical study for SIDS endpoint
13-MAY-2004 (7)

Type: flow through
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 14 day(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 86 - measured/nominal
LC50: > 86 - measured/nominal
Limit Test: yes

Method: OECD Guide-line 204 "Fish, Prolonged Toxicity Test: 14-day Study"
Year: 1997
GLP: yes
Test substance: other TS:hydrolyzed substanse prescribed as 1.1-1.4

Method: Statistical methods: Not used (because this study was limit

test)

Result:

-Nominal/measured Concentration:

Nominal concentration	Measured concentration(mg/l) (percentage of nominal) 0-day	7-day	14-day	Mean*
Control	<5	<5	<5	-
100.0	83 (83)	83 (83)	92 (92)	86 (86)

* Expressed as arithmetic means calculated

-Water Temperature: 23.7-24.1 ‹C

-Water Chemistry in test:

DO = 7.6-8.3 mg/l(>=60 % Oxygen saturation level)

-pH 6.3-6.6

pH values during a 14day flow through exposure of Medaka (Oryzias latipes) to hydrolysates of tetrahydromethyl-1,3-isobenzofurandione:

concentration (mg/l)	Measured pH 0-day	2-day	4-day	7-day	9-day	11-day	14-day
Control	7.9	7.9	7.7	7.8	8.0	7.9	8.0
100	6.4	6.4	6.3	6.5	6.6	6.5	6.3

-Cumulative mortality:

Nominal concentration (mg/l)	Cumulative number of dead fish mortality(%) vs time (day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

-LC50:

Exposure time	LC50
7days	> 86 mg/l
14days	> 86 mg/l

-Other effects : Toxic symptom : No toxic symptom observed

-NOEC >86 mg/l

Source: MOE, Japan 1997

Test condition:

-Test design : A limit test at 100 mg/l

-Test Organisms:

a)Size (length and weight):
length = 20-22 mm,
weight =0.15-0.19 g

b)Supplier/Source: obtained from commercial hatchery
(nango suisan center, shiga-pref. Japan)

c)Sensitivity to reference substance:96 hr LC50 of reference substance (CuSO4 5H2O) = 3.6 mg/l

-Test Condition:

a)Dilution Water Source: dechlorinated tap water

b)Dilution Water Chemistry:
hardness = 62 mg/l as CaCO3, pH = 7.9,
chlorine concentration <0.01 mg/l

c)Exposure Vessel Type:
5.0 l glass flow through aquarium

d)Nominal Concentration(as mg/l): 0 and 100
(Nominal concentration << water solubility(>1000 mg/l))

e)Vehicle/Solvent and Concentrations:

```
                    Solvent;Not used
                   f) Stock Solutions, Preparations and Stability:
                    Tetrahydromethyl-1,3-isobenzofuranedione was added in
                    dechlorinated tap water (1000 mg/l) and stirred more
                    than 60 min. The test solution was supplied continuously
                    by mixing the working solution and the dilution water
                    with the help of a mechanically operated quantitative
                    water-pump.
                   g)Number of Replicates: 1
                   h)Fish per Replicates: 10
                   i)Flow-through  Rate : 35 ml/min
                   j)Water temperature 22-26  degrees C
                    (measured 23.7-24.1  degrees C)
                   k)Intensity of Irradiation: room light
                   l)Photoperiod: 16h:8h light-dark cycle
                  -Analytical Method: HPLC (detection limit = 5 mg/l)
                  -Statistical Method:
                   a)Data Analysis: None
                   b)Method of Calculating
                    Mean Measured Concentrations :
                    arithmetic mean
Reliability:      (1)  valid without restriction
                  well conducted study, carried out by Sumika Technoservice
                  Co.
Flag:             Critical study for SIDS endpoint
13-MAY-2004                                                              (8)


4.2 Acute Toxicity to Aquatic Invertebrates

Type:             static
Species:          Daphnia magna  (Crustacea)
Exposure period:  48 hour(s)
Unit:             mg/l                    Analytical monitoring: yes
EC50:             = 130 - measured/nominal

Method:           OECD Guide-line 202
  Year:           1997
   GLP:           yes
Test substance:   other TS:hydrolyzed substance prescribed as 1.1-1.4

Method:           Statistical methods: Probit methods was used for EiC50
Result:           -Nominal/measured Concentration:
                    Nominal         Measured concentration(mg/l)
                  concentration          (percentage of nominal)
                    (mg/l)          0-hr     48-hr       Mean*
                  ---------------------------------------------------
                    Control           <5      <5       <5   (-)
                      32             31      31       31  (97)
                      56             48      49       49  (87)
                     100             85      88       87  (87)
                     180            140     140      140  (78)
                     320            270      #       270  (84)
                      * :Expressed as geometric means calculated
                      #: No measurement was made because all
                        Daphnia magna died before this observation time

                  -Water Temperature: 20.7-20.9 degrees C
                  -Water Chemistry in test:
                     pH 4.3-7.8
                     DO = 7.9-8.3 mg/l(>=60 % Oxygen saturation level)
```

-pH values during a 48 hr static exposure of Daphnia magna to hydrolysates of tetrahydromethyl-1,3-isobenzofurandione:

Measured concentration (mg/l)	pH 0-hr	pH 48-hr
Control	7.7	7.2
31	6.9	7.8
49	6.6	7.7
87	6.3	7.2
140	5.6	6.1
270	4.3	#

#: No measurement was made because all Daphnia magna were dead at this observation time

-Cumulative immobility:

Measured concentration (mg/l)	Cumulative number of Immobilized Daphnia (Percent immobility) 24-hr	48-hr
Control	0(0)	1(5)
31	0(0)	1(5)
49	0(0)	0(0)
87	0(0)	0(0)
140	2(10)	12(60)
270	20(100)	20(100)

-EiC50: 130 mg/l (48 hr) based on measured concentration

Exposure time (hr)	EiC50 (mg/l)	95 % confidence limits (mg/l)
24	180	140 - 270
48	130	87 - 270

-EC0: 87 mg/l (48 hr) based on measured concentration
-EiC100 (100% immobility): 270 mg/l (48 hr) based on measured concentration

Source: MOE Japan 1997

Test condition:
-Test Organisms:
a)Age at Study Initiation:<24 hr after hatching
b)Supplier/Source: Supplied from Sumika Tecnoservice Co.
c)Sensitivity to reference substance:
48 hr EC50 of reference substance (K2CrO4) = 0.80 mg/l
-Test Condition:
a)Dilution Water Source: dechlorinated tap water
b)Dilution Water Chemistry:
hardness = 62 mg/l as CaCO3
pH = 7.9,
chlorine concentration <0.01 mg/l
c)Exposure Vessel Type: 100 ml glass beaker
d)Nominal Concentration(as mg/l): 32, 56, 100, 180 and 320
(Nominal concentration << water solubility(>1000 mg/l))
e)Vehicle/Solvent and Concentrations:
Solvent; Not used
f) Stock Solutions Preparations and Stability:
Tetrahydromethyl-1,3-isobenzofuranedione added in decrorinated tap water (1000 mg/l) and stirred more than 60 min.
g)Number of Replicates: 4
h)Individuals per Replicates: 5
i)Renewal Rate of Test Water: water renewal; No
j)Water temperature: 19-21 degrees C
k)Intensity of Irradiation: room light

```
                  l)Photoperiod: 16h:8h light-dark cycle
                 -Duration of the Test: 48 hr
                 -Test Parameter     : immobility
                 -Analytical Method   : HPLC (detection limit = 5 mg/l)
                 -Statistical Method: Binominal
                  a)Data Analysis: Probit
                  b)Method of Calculating Mean Measured Concentrations:
                   geometric means
Reliability:     (1)  valid without restriction
                 carried out by Sumika Technoservice Co.
Flag:            Critical study for SIDS endpoint
13-MAY-2004                                                          (5)


4.3 Toxicity to Aquatic Plants e.g. Algae

Species:         Selenastrum capricornutum  (Algae)
Endpoint:        other: biomass and growth rate
Exposure period: 72 hour(s)
Unit:            mg/l                  Analytical monitoring: yes
NOEC:            = 27.5 - measured/nominal
EC10:            - measured/nominal
EC50:            = 64 -
NOEC growth rate(24-72h) :
                 = 27.5 - measured/nominal
EC50 growth rate (24-48h) :
                 = 55 - measured/nominal

Method:          OECD Guide-line 201  "Algae, Growth Inhibition Test"
  Year:          1997
   GLP:          yes
Test substance:  other TS:hydrolyzed substance prescribed as 1.1-1.4

Method:          Statistical methods: Bartlett test, One way ANOVA,
                 kruskal-wallis rank test and Dunnet's test were used for
                 NOEC
Result:          -Nominal/measured Concentration:
                  Nominal   Measured concentration (mg/l)
                  concentraton  (percentage of nominal)
                   (mg/l)     0-hr     72-hr
                 ----------------------------------------
                      0      <5       <5
                     10       8.7      9.0
                              (8.7)    (9.0)
                     18      15       15
                              (83.3)   (83.3)
                     32      27       28
                              (84.4)   (87.5)
                     56      48       49
                              (85.7)   (87.5)
                    100      85       87
                              (85.0)   (87.0)
                 -Water temperature: 23.5-23.6  degrees C
                 -Water chemistry in test:
                  pH=5.2-7.8 at start and 5.2-7.7 at end of the test (72hr).
                  High concentration group indicated lower pH value.
                 -Effect Data/element values:
                  Growth inhibition (comparison of area under growth curve)
                    EbC50(0-72 hr);       m =64mg/l  n =75mg/l
                    NOEC(0-72 hr) ;       m =27.5mg/l n =32mg/l
                  Growth inhibition (comparison of growth rates)
                    ErC50(24-48 hr);      m =55mg/l  n =64mg/l
```

NOEC(24-48 hr) ; m =43mg/l n =56mg/l
ErC50(24-72 hr); m =68mg/l n =79mg/l
NOEC(24-72 hr) ; m =27.5mg/l n= 32mg/l

- Biological observations

Nominal Concentration (mg/l)	Cell density (x 10E+4 cells/ml) 0-hr	24-hr	48-hr	72-hr
Control	1.00+/-0.00	3.50+/-0.31	20.7+/-0.80	135+/-4.00
10	1.00+/-0.00	3.72+/-0.11	21.1+/-0.40	151+/-9.00
18	1.00+/-0.00	3.79+/-0.05	22.1+/-0.10	156+/-1.00
32	1.00+/-0.00	3.87+/-0.10	21.3+/-0.90	147+/-10.0
56	1.00+/-0.00	3.77+/-0.15	21.5+/-0.40	112+/-1.00
100	1.00+/-0.00	1.17+/-0.04	1.35+/-0.19	2.12+/-0.27

(Each value represents the mean of three sample counts +/-S.D.)

Source: MOE Japan 1997

Test condition:
-Test organisms
strain: ATCC22662
Laboratory culture: OECD medium
Method of cultivation: Shaking (100 rpm)
Controls: OECD medium.
EC50 of potassium dichromate was 0.42 mg/l.
-Test Conditions
Open system
Test temperature range: 23.5-23.6 ‹C
Growth/test medium: OECD medium
Shaking: 100 rpm
Dilution water source: OECD medium
Exposure vessel type:
100 ml medium in a 500 ml conical flask with a cap which allow ventilation.
Stock solutions preparation:
Test chemical was dissolved in OECD medium and stirred more than 60 min. By this procedure, test chemicals was hydrolyzed.
Light levels and quality during exposure:
4400-5000 lx, continuous
-Test design:
Number of replicates: Triplicate
Concentrations: 0, 10, 18, 32, 56 and 100 mg/l
Initial cell number in cells/ml: 1x10E+4
- Method of calculating mean measured concentrations :
arithmetic mean

Growth curves: Logarithmic growth until end of the test (72 hr)
Percent biomass/growth rate inhibition per concentration: IA=(Ac-At)x100/Ac
Ac: Area under the growth curve of control
At: Area under the growth curve of each test group
Observations: All test groups (0-56 mg/l, except 100 mg/l) showed normal and similar growth that of control.

Reliability: (1) valid without restriction
carried out by Sumika Technoservice Co.

Flag: Critical study for SIDS endpoint

13-MAY-2004 (4)

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l Analytical monitoring: yes
LOEC: = 3.5 - measured/nominal
EC50: = 9.2 - measured/nominal
LC50 for parental Daphnia :
> 110 - measured/nominal

Method: OECD Guide-line 202, part 2 "Daphnia sp., Reproduction Test"
Year: 1997
GLP: yes
Test substance: other TS:hydrolyzed substance prescribed 1.1-1.4

Method: Statistical methods: Binominal method was used for ErC50
Result: RESULTS:EXPOSED
-nominal/measured concentrations:

Nominal concentration (mg/l)	Measured concentrations (Percent of nominal) 9day new*	12day old#	16day old#	19day old#	Time Weighted Mean
0	<0.2	<0.2	<0.2	<0.2	<0.2
1.3	1.1 (82)	0.95 (73)	0.85 (66)	0.87 (67)	0.94 (72)
4.1	3.4 (83)	3.4 (83)	3.5 (85)	3.5 (86)	3.5 (84)
13	11 (84)	11 (83)	11 (83)	11 (85)	11 (84)
41	34 (83)	35 (84)	34 (84)	36 (87)	35 (84)
130	110 (83)	110 (84)	110 (82)	110 (84)	110 (83)

*:Freshly prepared test solution
#:Test solutions 3 days after freshly prepared

-effect data
NOEC (21 d, reproduction) 0.94 mg/l
LOEC (21 d, reproduction) 3.5 mg/l
EC50 (14 d, reproduction) 2.3 mg/l
EC50 (21 d, reproduction) 9.2 mg/l
LC50 for parental Daphnia (14 d and 21 d) >110 mg/l
;calculated based on measured concentrations
- Biological observations
Cumulative numbers of dead parental Daphnia Days

Group	0-10,11,	12,	13,14,15,	16,17,	18,19,	20,21
Control	0,	0,	0, 0, 0,	0,	1, 1,	2, 2, 3, 4
0.94mg/l	0,	0,	0, 0, 1,	2,	2, 2,	2, 3, 3, 4
3.5 mg/l	0,	0,	0, 1, 1,	2,	2, 2,	3, 4, 7, 9
11 mg/l	0,	0,	1, 1, 1,	1,	1, 1,	2, 3, 4, 6
35 mg/l	0,	0,	1, 2, 2,	3,	4, 4,	4, 4, 6, 6
110 mg/l	0,	1,	2, 2, 2,	3,	3, 4,	5, 6, 7, 7

Mean cumulative numbers of young produced per adult:

Group	Days 0-6,	7,	8,	10,	12,	14
Control	0,	3.7,	3.7,	4.8,	5.6,	18.2
0.94 mg/l	0,	2.9,	2.9,	6.3,	7.1,	18.6
3.5 mg/l	0,	1.2,	1.2,	1.8,	2.0,	3.3
11 mg/l	0,	0.3,	0.3,	1.3,	1.4,	1.4
35 mg/l	0,	0.1,	0.1,	0.2,	0.2,	0.3
110 mg/l	0,	0,	0,	0,	0,	0.1

Mean cumulative numbers of young produced per adult:

Group	Days 16,	18,	20,	21
Control	39.6,	47.7,	73.4,	73.4
0.94 mg/l	41.6,	50.5,	73.7,	73,7
3.5 mg/l	24.5,	28.8,	53.8,	53.8
11 mg/l	21.7,	25.9,	33.4,	33.4
35 mg/l	11.3,	19.0,	22.6	22.6
110 mg/l	0.5,	14.1,	22.2,	23.0

RESULTS:TEST WITH REFFERENCE SUBSTANCE
-results: K2CrO7 pure grade:
48 hr EiC50 = 0.80mg/l(immobility data)

Source: MOE Japan 1997

Test condition:
-Test organisms: Daphnia magna
Source: Supplied by NIES (Japan).
Age at study initiation: Juveniles within 24 hr old.
Control group: Yes
-Test conditions
Stock solutions preparation and stability:
Test chemical was dissolved in dechlorinated tap water and stirred more than 60 min. By this procedure, test chemical was hydrolyzed.
Test temperature range: 20.2-20.8 degrees C
Exposure vessel type: 1000 ml test solution in a 1000 ml glass beaker; 4 beakers per treatment
Dilution water source: Dechlorinated tap water
Dilution water chemistry: Hardness: pH=7.9, 62 mg/l as CaCO3
Lighting: room light, 16h: 8h light-darkness cycle
Water chemistry in test: DO= 7.2-8.8 mg/l; pH=6.1-8.2
Feeding: Chlorella vulgaris, 0.1-0.2 mgC/day/individual
-Element (unit) basis: Mean cumulative numbers of juveniles produced per adult (reproduction)
-Test design: Number of replicates=4;
individuals per replicate=10;
concentrations: 0, 1.3, 4.1, 13, 41 and 130 mg/l,
because EC50 (24 h Immobilization test) was 130 mg/l
-Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean, etc.):
time weighted mean
-Exposure period: 21 d
-Analytical monitoring: At day 9, 82-84% of the nominal concentration at preparation; 73-84% just before the renewal of the test water. At day 16, 66-85% of the nominal concentration at preparation; 67-87% just before the renewal of the test water.

Reliability: (1) valid without restriction
carried out by Sumika Technoservice Co.
Flag: Critical study for SIDS endpoint
13-MAY-2004 (6)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 5
Vehicle: other: corn oil (10ml/kg)
Doses: 0(Vehicle), 500, 1000 and 2000 mg/kg/day (in corn oil)
Value: > 2000 mg/kg bw

Method: OECD Guide-line 401 "Acute Oral Toxicity"
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: -Body weight:
The body weight of treatment groups of rats for males and females were not different from controls except in males and females of the 2000 mg/kg group was decreased at the day after administration.
-Food/water consumption: Not specified.
-Clinical signs:
hypoactivity, bradypnea and prone position were observed in males and females of the 2000 mg/kg group on the day of administration.
-Haematology: Not done.
-Biochem : Not done.
-Ophthalmologic findings: Not examined.
-Mortality and time to death:
No deaths prior to schedule termination.
-Gross pathology incidence and severity:
At necropsy, thickening of the forestomach mucosa was observed in males and females of the 1000 and 2000 mg/kg group.
Adhesion of forestomach and liver was noted in one female of the 2000 mg/kg group.
-Organ weight changes: Not done.
-Histopathology (incidence and severity):
Squamous hyperplasia and granulomatous inflammation in submucosa of the forestomach were observed, and a squamous hyperplasia was also noted.

Squamous hyperplasia of the forestomach
1000mg/kg : male (2/5), female (1/5)
2000mg/kg : male (5/5), female (5/5)
(Squamous hyperplasia and granulomatous inflammation was observed in representative case of in males and females of the 1000 and 2000mg/kg group)
Adhesion of forestomach and liver and a foreign body granuloma in the adhesion area
2000mg/kg : female (1/5)

LD50: Male: >2000 mg/kg ; Female : >2000 mg/kg
Source: MHW, Japan

Test condition: -Test Subjects:
Age at study initiation:
Purchased 5 week old animals,
administration was initiated at 6 week old.
Weight at study initiation:
172.1-193.1 g for males,
125.4-139.9 g for females (at 6 week old)
No. of animals per sex per dose:
5 per sex per dose group
-Study Design:
Vehicle: Corn oil (10 ml/kg)
Satellite groups and reasons they were added: None
Clinical observations performed and frequency:
General condition was observed once a day.
Each rat was weighed immediately prior to treatment,
the day 2, 4, 6, 8, 11 and 15 after administration.
Reliability: (1) valid without restriction
carried out by Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd.
Flag: Critical study for SIDS endpoint
12-JAN-2003 (20)

Type: LD50
Species: rat
Strain: Crj: CD(SD)
Sex: male/female
Vehicle: other: undiluted
Doses: 0(water 5.3ml/kg),1000, 1600, 2000, 3200, 5000 and 6400mg/kg
Value: = 1900 mg/kg bw

Method: other: not cited
Year: 1980
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Carried out by Huntingdon Research Center, Huntington, Cambridgeshire, ENGLAND
Result: Death occurred amongst rats treated at 1600 mg/kg and above. Old study (in 1980).
Source: Hitachi Chemical Co., Ltd. unpublished report
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
18-JUL-2002 (12)

Type: LD50
Species: rat
Strain: other:Donryu
Sex: male
No. of Animals: 6
Vehicle: other: Olive oil
Doses: 1160, 1390, 1660, 2000 and 2400mg/kg
Value: = 2102 mg/kg bw

Method: other: not cited
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Old study with poor observation.
Result: LD50 : Male; 2102 mg/kg
Source: Hitachi Chemical Co., Ltd. unpublished report.
Reliability: (3) invalid

07-JUN-2002

Type: LD50
Species: rat
Strain: no data
Sex: no data
Value: = 2.14 ml/kg bw

Method: other: not cited
GLP: no data
Test substance: other TS

Test substance: CAS 26590-20-5
Reliability: (3) invalid
08-JAN-2003 (24)

Type: LD50
Species: rat
Value: = 2140 mg/kg bw

Method: other
GLP: no data
Test substance: other TS:CAS No.26590-20-5

Source: Lonza SpA Polymers and Additives Scanzorosciate
Reliability: (4) not assignable
08-JAN-2003

Type: LD50
Species: mouse
Strain: other: dd
Sex: male
No. of Animals: 10
Vehicle: other: Olive oil
Doses: 920, 1100, 1330, 1590, 1900, 2280, 2720mg/kg
Value: = 1707

Method: other: not cited
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Old study with poor observation.
Result: LD50 : Male; 1707 mg/kg
Source: Hitachi Chemical Co. Ltd., unpublished report.
Reliability: (3) invalid
11-JUN-2002

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Value: > 2000 mg/kg bw

Method: OECD Guide-line 402 "Acute dermal Toxicity"
Year: 1987
GLP: yes
Test substance: no data

Remark: Original report is not availavle.
Source: Lonza SpA Polymers and Addititives Scanzorosciate
Reliability: (4) not assignable
09-JAN-2003 (16)

Type: LD50
Species: rabbit
Value: = 1.41 ml/kg bw

Test substance: other TS

Source: Lonza SpA Polymers and Additives Scanzorosciate
Test substance: CAS No.26590-20-5
Reliability: (3) invalid
09-JAN-2003 (24)

Type: other
Species: rabbit
Sex: no data
Doses: 0.4 ml and 2 ml/animal

Method: other
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Old study with poor observation.
Result: 0.4 ml/animal : No change was observed.
2.0 ml/animal : No change was observed.
Reliability: (3) invalid
15-JUL-2002 (10)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Strain: other: Donryu
Sex: male
No. of Animals: 6
Vehicle: other: undiluted
Route of admin.: i.p.
Value: = 255 mg/kg bw

Method: not cited
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Old study with poor observation.
Result: LD50 : Male;255 mg/kg
Source: Hitachi Chemical Co. Ltd., unpublished report
Reliability: (3) invalid
15-JUL-2002

Type: LD50
Species: mouse
Strain: other: dd
Sex: male
Route of admin.: i.p.
Value: = 222 mg/kg bw

Method: not cited
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Old study with poor observation.
Result: LD50 : Male;222 mg/kg
Source: Hitachi Chemical Co. Ltd., unpublished report
Reliability: (3) invalid

07-JUN-2002

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: no data
No. of Animals: 6
PDII: 3.5

Method: other:The Code of Federal Regulations, Title 16, Section 1500.41
Year: 1980
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Source: Hitachi Chemical Co., Ltd.
Test substance: Hitachi Chemical Co., Ltd. purity not stated.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
19-APR-2004 (11)

Species: rabbit

Result: score 1 on irritation on uncovered rabbit belly.
Reliability: (3) invalid
18-JUL-2002 (24)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 other: ml/eye
Comment: not rinsed
No. of Animals: 1
Result: irritating

Method: other
Year: 1969
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: One minute after pouring 0.1 ml, cornea cloudy and eye ball opaque. In 24 hr, iris congested but no bleeding or edma. On the 10th day, recovered to half eye, reflection to light normalized, and congestion extinguished. When 0.01 ml was poured, recovered to half eye in 24 hr.

Test substance: Hitachi Chemical Co., Ltd., purity not stated.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

15-JUL-2002 (10)

Species: rabbit

Result: Score 9 on a 10 point scale.
Reliability: (3) invalid
18-JUL-2002 (24)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: gavage
Exposure period: Males; for 49 days Females; from 14 days before mating to day 3 of lactation
Frequency of treatment: one administration/day
Doses: 0(Vehicle), 30, 100 and 300 mg/kg/day (in corn oil)
Control Group: yes, concurrent vehicle
NOAEL: = 100 mg/kg

Method: OECD combined study TG422
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: -Body weight: No stat. sig. difference from controls.
-Food consumption: No stat. sig. difference from controls except one case (male 30 mg/kg, day 49, increase in consumption).
-Clinical signs (description, severity, time of onset and duration):
Salivation was observed in 4-9(/12) animals at male 300 mg/kg on and after day 36. Salivation was observed immediately after administration, and continued about 30 min.
Hematology: No stat. sig. difference from controls.
Biochem:
Males: Decrease of total cholesterol and BUN, increase of triglyceride at 300 mg/kg ($p<0.05$). Decrease of A/G ratio at 100 mg/kg ($p<0.05$).

Dose level (mg/kg/day)	0	30	100	300
No. of animals	12	12	12	11#
Total cholesterol (mg/dl, Mean+/-SD)	67 +/-14	60 +/-9	64 +/-9	55 +/-6*
BUN (mg/dl, Mean+/-SD)	16.9 +/-2.2	16.6 +/-2.3	16.4 +/-2.3	14.8 +/-1.3*
Triglycerides (mg/dl, Mean+/-SD)	47+/-21	54+/-16	49+/-14	73+/-28*
A/G ratio	1.98	2.02	1.80	1.91

```
                    +/-0.18    +/-0.16     +/-0.17*   +/-0.12
 *: p<0.05(sig. different from control)
 #:one animal was dead by accident at administration

-Ophthalmologic findings: Not examined
-Mortality and time to death:
    Three animals (male and female of 300mg/kg group
    and male of 30mg/kg group) is died by the accident
    at administration.
-Gross pathology incidence and severity:
 hyperplasia(male:11/11, female 9/11) at forestomach mucosa
 (in 300mg/kg, terminal sacrifice)
-Organ weight changes:
  Male:  increase in kidney weight and adrenal weight
         at 100 mg/kg (absolute) (p<0.05)
          increase in adrenal weight at 300 mg/kg
         (relative) (p<0.05)
  Female:No stat. sig.  difference from controls

Males
Dose level          0          30       100      300
(mg/kg/day)
-----------------------------------------------------
Body weight       516.5      530.4    530.9    492.8
(g, Mean+/-SD)   +/-30.2   +/-18.6   +/-27.4   +/-35.0

Absolute weight
Kidney             2.99       3.00      3.17     3.05
(g, Mean+/-SD)    +/-0.21   +/-0.09   +/-0.24*  +/-0.27

Adrenal            53.2       57.3      60.8     60.3
(mg, Mean+/-SD)   +/-6.2    +/-4.7    +/-5.9*  +/-13.4

Relative weight
Adrenal            10.3       10.8      11.3     12.2
(mg%, Mean+/-SD)  +/-0.9    +/-1.1    +/-1.2   +/-2.4*
        *: p<0.05(sig. different from control)

-Histopathology (incidence and severity):
Male:
Forestomach:
                Dose level (100 mg/kg/day)
                Terminal
                sacrifice
-----------------------------------------------------

Number of        12
 animals

Organs and
  findings          -  +   ++  +++

Forestomach

 Squamous          11  1    0   0
 hyperplasia


Male:
Forestomach:  Increased mucosa changes at 300 mg/kg.

                Dose level (300 mg/kg/day)
```

	Terminal sacrifice				Imminent sacrifice/Dead				Total			
Number of animals	11				1				12			
Organs and findings	-	+	++	+++	-	+	++	+++	-	+	++	+++
Forestomach												
Squamous hyperplasia	0	1	10	0	1	0	0	0	1	1	10	0
Vacuolar change, epithelium	1	10	0	0	1	0	0	0	2	10	0	0
Inflammation, granulomatous, submucosa	0	10	1	0	1	0	0	0	1	10	1	0
Edema, epithelium to submucosa	1	10	0	0	0	0	1	0	1	10	1	0
Cellular infiltration, epithelium to submucosa	11	0	0	0	0	1	0	0	11	1	0	0
Lung												
Fatty droplet, alveoli	11	0	0	0	0	1	0	0	11	1	0	0
Hemorrhage and edema	11	0	0	0	0	0	1	0	11	0	1	0

Grade: - none, + mild, ++ moderate, +++ marked

Integument system:
Erosion (grade; mild, 1/12 animals) at control.

Female:
Forestomach: Increased mucosa changes at 300 mg/kg.

Dose level (300 mg/kg/day)

	Terminal sacrifice				Imminent sacrifice/Dead				Total			
Number of animals	11				1				12			
Organs and findings	-	+	++	+++	-	+	++	+++	-	+	++	+++
Forestomach												
Squamous hyperplasia	1	9	0	0	1	0	0	0	2	9	0	0
Inflammation, granulomatous, submucosa	3	7	0	0	1	0	0	0	4	7	0	0
Erosion	8	2	0	0	0	1	0	0	8	3	0	0

Esophagus															
Hemorrhage, mucosa layer	0	0	0	0	0	1	0	0	0	1	0	0			
Cellular infiltration, mucosal layer															
Lung															
Fatty droplet, alveoli	11	0	0	0	0	1	0	0	11	1	0	0			
Thymus															
Atrophy	10	1	0	0	0	1	0	0	10	2	0	0			
Kidney															
Necrosis, tubular epithelium, cortex, Clocal	11	0	0	0	0	1	0	0	11	1	0	0			
Mammary gland															
Adenocarcinoma	0	1	0	0	0	0	0	0	0	1	0	0			

Grade: - none, + mild, ++ moderate, +++ marked

NOAEL : Male ; 100 mg/kg bw
Female ; 100 mg/kg bw
Relative and/or absolute adrenal and/or kidny(s) weight increase was obserbed in male 100 and/or 300 mg/kg group,
but there is no histopathological change was obserbed, so we the author exclude this obserbation. Squeamous hyperplasia was obserbed in only one male of 100 mg/kg group, so we the author exclude this obserbation.
Therefore, we decided the NOAEL as 100 mg/kg in male.

Source: MHW, Japan

Test condition:
-Test Subjects:
Age at study initiation:
Purchased 9 week old animals, administration was initiated at 10 week old.
Weight at study initiation:
356.3 - 394.4 g for males,
213.5 - 252.9 g for females (at 10 week old)
No. of animals per sex per dose:
12 per sex per dose group
-Study Design:
Vehicle: Corn oil (5ml/kg)
Satellite groups and reasons they were added: None
Clinical observations performed and frequency:
General condition was observed once a day,
body wt. and food consumption were determined twice a week.
Hematology and biochemistry for males only at time of necropsy after 49 days of chemical exposure
Organs examined at necropsy:
organ weight:
brain, heart, lung, liver, kidney, spleen, adrenal, thymus, testes, epididymis, ovary
microscopic:
all animals in control and 300 mg/kg;
any organs which have histopathological changes and stomach of all animals. Unfertilised animals in any groupes; testes, epididymis and ovary

Reliability: (1) valid without restriction
carried out by Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd.
Flag: Critical study for SIDS endpoint
13-MAY-2004 (17)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium, TA100, TA1535, TA98, TA1537, Escherichia coli Wp2 uvrA
Concentration: -S9 mix; 0, 62.5, 125, 250, 500, 1000, 2000 ug/plate
+S9 mix; 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
Cytotoxic Concentration: without metabolic activation(-S9mix)
500 ug/plate (TA1535),
1000 ug/plate (TA100, TA98, TA1537),
2500 ug/plate (WP2)
with metabolic activation(+S9mix)
5000 ug/plate (TA100, TA1537)
Metabolic activation: with and without
Result: negative

Method: other: Guidelines for screening Mutagenicity testing of Chemicals(Japan) and OECD Test Guideline 471 and 472
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: This chemical did not induce mutations in the S. typhimurium and E. coli strains.
Toxicity was observed at 150 ug/plate(TA100, TA1537), 250 ug/plate (TA1535, TA98, WP2) without an S9 mix, and at 150 ug/plate (TA100, TA1537), 250 ug/plate(TA1535, TA98), 500 ug/plate (WP2) with an S9 mix.

Genetic effects:
Salmonella typhimurium TA100, TA1535, TA98, TA1537
Without metabolic activation: negative
With metabolic activation : negative
Escherichia coli WP2 uvrA
Without metabolic activation: negative
With metabolic activation : negative

Detail is shown in APPENDIX 2.
Source: MHW, Japan
Test condition: Procedures : Pre-incubation method
Solvent : DMSO
Positive controls : -S9 mix,
2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2),
Sodium azide (TA1535) and 9-Aminoacridine (TA1537)
+S9 mix,
2-Aminoanthracene (five strains)
Doses : -S9 mix;
0, 62.5, 125, 250, 500, 1000, 2000 ug/plate
+S9 mix;
0, 156, 313, 625, 1250, 2500, 5000 ug/plate
S9 : Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test: 3
Number of replicates : 2

Reliability: (1) valid without restriction
carried out by Hatano Research Institute, Food and Drug Safety Center
Flag: Critical study for SIDS endpoint
29-JAN-2003 (18)

Type: Chromosomal aberration test
System of testing: CHL/IU cell
Concentration: contenuous treatment (with and without S9)
: 0.075, 0.15, 0.30 and 0.60 mg/ml
pre incubation (without S9)
: 0.050, 0.10, 0.20 0.40 and 0.80 mg/ml
pre incubation (with S9)
: 0.11, 0.21, 0/43, 0.85 and 1.7 mg/ml
Cytotoxic Concentration: Without metabolic activation
(continuous treatment) : LC50=0.3 mg/ml
Without metabolic activation
(short-term treatment) : LC50=0.4 mg/ml
With metabolic activation
(short-term treatment) : LC50=1.0mg/ml
Metabolic activation: with and without
Result: ambiguous

Method: other: Japanease TG and OECD TG 473
GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Result: Structural chromosomal aberrations was not induced.
Polyploidy was observed with 0.3 mg/ml 48 hr continuous treatment and with 0.11-0.43 mg/ml (all concentrations) and short-term treatment with an exogeneous metabolic activation system.
Genotoxic effects:
clastogenicity
Without metabolic activation : negative
With metabolic activation : negative
polyploidy
Without metabolic activation : ambiguous
With metabolic activation : ambiguous

Detail is shown in APPENDIX 2_11070443.doc
Source: MHW, Japan
Test condition: For continuous treatment, cells were treated for 24 or 48hr without S9mix.
For short-term treatment, cells were treated for 6 hr with and without S9mix and cultivated with fresh media for 18 hr.
Solvent :Dimethylsulfoxide
Positive Controls:Mitomycin C for without S9mix treatment
Cyclophosphamide for with S9mix treatment
Doses :Without S9mix (continuous treatment):
0, 0.075, 0.15 and 0.3 mg/ml
Without S9mix (short-term treatment):
0, 0.05, 0.10 and 0.20 mg/ml
With S9mix (short-term treatment)
0, 0.11, 0.21 and 0.43 mg/ml
S-9 :Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test :2
Attached doc.: 11070443_APPENDIX2.doc
Reliability: (1) valid without restriction

carried out by Hatano Research Institute, Food and Drug Safety Center
Flag: Critical study for SIDS endpoint
13-MAY-2004 (19)

5.6 Genetic Toxicity 'in Vivo'

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

5.8.3 Toxicity to Reproduction, Other Studies

Type:	other: OECD TG 422 -Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
In Vitro/in vivo:	In vivo
Species:	rat
Strain:	Crj: CD(SD) Sex: male/female
Route of administration:	gavage
Exposure period:	Male; for 49 days from 2 weeks prior to mating, Female; from 2 weeks prior to mating to day 3 of lactation throughout mating period (max; 14 day) and pregnancy.
Frequency of treatment:	one administration/day
Duration of test:	Male : for 49 days, Female : for 17-31 days
Doses:	0(Vehicle), 30, 100 and 300 mg/kg/day (in corn oil)
Control Group:	yes, concurrent vehicle

Method: other: OECD TG 422 -Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL foetal toxicity:
NOAEL: 300 mg/kg/day
Actual dose received by dose level by sex if available:
0, 30, 100 and 300 mg/kg/day for both sexes
Maternal data with dose level (with NOAEL value):
At 30 and 100 mg/kg, there was a tendency for decrease of estrus frequency, but at 300 mg/kg, no statistically significant effects were observed.

Foetal data with dose level (with NOAEL value):
At 30 and 100 mg/kg, statistically significant decrease of birth index was observed, and at 300 mg/kg, stillborn was observed only one animal (not statistically significant).
At 100 mg/kg, total litter loss in two dams were observed.
At 300 mg/kg, no statistically significant effects were observed, but there was a tendency for decrease of developmental parameters (total number of pups born, delivery index and live birth index).

Dose level (mg/kg/day)	0	30	100	300
No. of dams	11	11	11	10
No. of corpora lute(Mean+/-SD)	22.18 +/-0.40	22.27 +/-0.47	22.09 +/-0.30	22.30 +/-0.48
No. of implantations	183	188	188	162
(Mean+/-SD)	16.64 +/-1.63	17.09 +/-1.30	17.09 +/-0.94	16.20 +/-1.03
No. of litter	171	178	181	154
(Mean+/-SD)	15.55 +/-2.58	16.18 +/-1.25	16.45 +/-0.69	15.40 +/-1.65
Gestation index	100	100	100	100
No. of stillborns				
Male	0	4	3	4
Female	0	4	6	6
Total (%)	0 (0)	8 (5.06)*	9 (5.33)*	10 (6.76)
No. of live newborns	162	150	160	138
(Mean+/-SD)	14.73 +/-2.65	13.64 +/-1.43	14.55 +/-0.82	13.80 +/-2.53
Birth index	94.74	84.27*	88.40*	89.61
Sex ratio of live newborns	0.98	0.90	1.08	0.86
(male/female)	(80/82)	(71/79)	(83/77)	(64/74)
Body weight of live pups (g) (Mean+/-SD) on day 0				
Males	6.2 +/-0.5	6.1 +/-0.4	6.0 +/-0.4	6.3 +/-0.5
Females	9.4 +/-1.2	9.5 +/-1.1	9.1 +/-0.7	9.9 +/-0.9
Body weight of live pups (g) (Mean+/-SD)on day 4				
Males	6.0 +/-0.4	5.9 +/-0.4	5.8 +/-0.3	6.0 +/-0.5
Females	9.0 +/-1.3	9.2 +/-1.1	8.8 +/-0.5	9.5 +/-1.0
Viability index	98.15	94.00	81.88	93.48
No. of external anomalies	0	0	0	0

Gestation index =(Number of dams with live newborns
/Number of pregnant females) X 100
Birth index = (Number of newborns
/Number of implantations) X100
Viability index = (Number of live newborns on day 4
after birth/Number of live newborns) X100
*:P<0.05 significantly different from control
Background level of stillborn : 0-14.84%

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                  Background level of birth index : 80.98-96.61%
Source:           MHW, Japan
Test condition:   -Test Subjects:
                  Age at study initiation:
                    Purchased 9 week old animals, administration was
                    initiated at 10 week old.
                  Weight at study initiation:
                    356.3 - 394.4 g for males,
                    213.5 - 252.9 g for females
                  No. of animals per sex per dose:
                    12 per sex per dose group
                 -Study Design:
                    The animals were sacrificed on the day 4 of lactation
                    for females.
                  Vehicle: corn oil
                  Satellite groups and reasons they were added: none
                  Mating procedures:
                    Male/female per cage; 1/1, length of cohabitation;
                    at the most 14 days, until proof of pregnancy
                    (formation of vaginal closing or sperm detection in
                 vagina)
                  Clinical observations performed and frequency:
                    Parent: General appearance once a day
                    Pups  : Body weight (at day of birth and day 4 after
                            birth), sex, surface abnormality at day of
                            birth.
                    Hematology, biochemistry and urinalysis for males only
                    at time of necropsy after 49 days of chemical exposure
                  Organs examined at necropsy:
                    Parent:
                     organ weight: brain, heart, lung, thymus, liver,
                                   spleen, kidney, adrenal, testis,
                                   epididymis, ovary.
                     microscopic: all animals in control, 300 mg/kg group;
                                  brain, pituitary gland, eyeball,
                                  thyroid gland, parathyroid gland, thymus,
                                  heart, lung, liver, kidney, adrenal,
                                  spleen, stomach, small intestine,
                                  large intestine, pancreas,
                                  urinary bladder, bone marrow, ovary,
                                  uterus, vagina, mammary gland.
                     Unfertilized animals in any groups;
                                  testes, epididymis and ovary

                    Dams: full macroscopic examinations on all of pups
                     Parameters assessed during study:
                     Female: Body wt. (twice a week before mating,
                             day 0, 4, 7, 10, 14, 17 and 21 after mating ),
                             food consumption (same day of body wt. ),
                             No. of pairs with successful copulation,
                             copulation index (No. of pairs with successful
                             copulation/No. of pairs mated x 100),
                             pairing days until copulation,
                             No. of pregnant females,
                             fertility index = (No. of pregnant animals x
                             100/No. of pairs with successful copulation),
                             No. of corpora lutea, No. of implantation
                             sites, No. of living pregnant females,
                             No. of pregnant females with parturition,
                             gestation length, No. of pregnant females with
                             live pups on day 0, gestation index (No. of
                             females with live pups x 100/No. of living
```

pregnant females), delivery index (No. of pups born x 100/No. of implantation sites), No. of pups alive on day 0 of lactation, live birth index (No. of live pups on day 0 x 100/No. of pups born), sex ratio (Total No. of male pups/Total No. of female pups), No. of pups alive on day 4 of lactation, body wt. of live pups (on day 0 and 4)

Conclusion: As for reproductive performance, no effects related to the test article were observed on the estrous cycle, numbers of corpora lutea and implantations, copulation index or fertility indices. Examination at delivery and during the lactation period revealed, no effects related to the test article in terms of gestational days, litter size and live newborns, gestation index, stillborn index, birth index, sex ratio, body weights of offspring at birth and at day 4 after birth, or viability index on day 4. No external anomalies were apparent. The NOAEL is considered to be 300mg/kg/day for reproductive performance of parents and for development of offspring.

Reliability: (1) valid without restriction
carried out by Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd.

Flag: Critical study for SIDS endpoint

13-MAY-2004 (17)

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Human

Result: A method for the determination of methyltetrahydrophetalic acid(MTHP acid), a metabolite of tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) in human urine was developed. The investigated MTHP acid was obtained by hydrolysis of commercial MTHPA mixture (Ciba-Geigy), composed three major isomers.
These isomers were synthesized and identified as 3-methyl-delta-4-tetrahydrophthalicanhydride, 4-methy-delta-4-tetrahydrophthalic anhydride and 4-methyl-delta-3-tetrahydrophthalic anhydride.
The urine was worked up by a liquid-solid extraction technique using C18 sorbent columns. Esterification was performed with methanol and boron trifluolide.
The derivative in toluene was analyzed with capillary gas chromatography and selected ion monitoring.
Deuterium-labeled MTHP acid was used as internal standard.
The intra-assay precision for the overall method was between 4 and 8% in the range 3-110 ng/l and the inter-assay precision was between 4 and 7% in the range 3-110 ng/ml.
The total recoveries of the MTHPA acid at 19 and 190 ng/ml were 94 and 97%, respectively. The detection limit was <2 ng/ml for each of three isomers giving a total detection limit for the three isomers was <6 ng/ml. Urine samples were collected from ten volunteers who were presumed to be exposed MTHPA at an 8-h time weighted average of 11 ug/m3. All urine was collected during the 24 hr in 4 hr samples during the daytime and 7 hr samples during the night.

Assuming an inhaled volume of 10 m3 during a working day about 70% of the inhaled dose was excreted in urine as MTHP acid. The half times in the body were estimated as 3, 3 and 6 hr for
3-methyl-3-tetrahydrophthalic acid,
4-methyl-4-tetrahydrophthalic acid and
4-methyl-3-tetrahydrophthalic acid, respectively.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
08-JAN-2003 (15)

Type of experience: Human

Result: The patient was a man 22 years old. He had a heredity of rhinitis and had reacted since childhood with rehinitis while close contact with cats. He worked in the plant producing barrels for rocket guns from epoxy resin containing tetrahydromethyl-1,3-isobenzofuranedione (MTHPA).
He worked most of time in the winding department. The time-weighted MTHPA exposure at this site was 100 ug/m3. About 4 months after beginning his job, he experienced symptoms of nasal secretion and congestion during work. Some time later he developed chest tightness, a continuous productive cough and wheezing. He was transferred to another department, with low exposure to MTHPA, he had minor symptoms.
In a skin prick test, he was positive to a conjugate of MTHPA and human serum albumin(HAS), but negative to phthalic acid and HAS.
None of 34 unexposed reference workers in a nearby factory were positive to MTHPA-HAS.
Thus, his disease was caused by contact with MTHPA and it seems likely that the symptoms was caused by an IgE-mediated allergy.

17-JUL-2002 (23)

Type of experience: Human

Result: A group of 145 workers exposed to tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) was investigated. They were handled an epoxy resin with MTHPA as
a hardener in a plant, since 1983. Specific IgE antibodies (RAST) to a conjugate between MTHPA and human serum albumin (HAS) were statistically significantly increased in exposed group. Twenty-three exposed workers were also skin-prick test positive to MTHPA-HAS. Workers were divided into three different categories, according to their exposure level. The average exposure level at the time of the investigation were, in zone I 85 ug/m3, in zone II 14 ug/m3, and in zone III 10ug/m3. There was association between exposure intensity and RAST-positive persons. No association between sensitization and either atopy or smoking was found. There was association between exposure intensity and specific IgG antibodies. Specific IgG4 antibodies were closely related to specific total IgG. These findings demonstrate that MTHPA is a sensitizing agent at low levels of exposure.

15-JUL-2002 (27)

Type of experience: Human

Result: The outcome of immunologic tests of antibodies directed against hapten conjugates of three organic acid anhydrides and human serum albumin (HAS) has been studied in workers exposed to phthalic acid (PA), tetrahydromethyl-1,3-isobenzofuranedione (MTHPA), hexahydrophthalic anhydride (HHPA), methylhexahydrophthalic anhydride (MHHPA) and maleic anhydride (MA). There was a good correlation between skin prick test and RAST. The specific antibodies in workers exposed to either MTHPA or HHPA/MHHPA showed a marked cross-reactivity to MTHPA-HSA, HHPA-HAS and MHHPA-HAS as proven by skin prick test, RAST and RAST inhibition.

18-JUL-2002 (26)

Type of experience: Human

Result: One hundred and forty four current and 26 former workers in a plant producing barrels for rocket guns were reported. Time weighted average air concentration of tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) in working place was up to 150 ug/cu.m. Workers showed higher frequencies of work related symptoms from the eyes (31 vs 0%; $p<0.001$), nose (53 vs 9%; $p<0.001$), pharynx (26 vs 6%; $p<0.01$), and asthma (11 vs 0%; $p<0.05$) than controls. They had higher rates of positive skin prick test to a conjugate of MTHPA and human serum albumin (16 vs 0%; $p<0.01$), and more had specific IgE and IgG serum antibodies (18 vs 0%; $p<0.01$ and 12 vs 0%; $p<0.05$ respectively). There ware statistically significant exposure-response relations between exposure and symptoms.

18-JUL-2002 (22)

Type of experience: Human

Result: Fourty three workers exposed tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. Ten workers sensitized to MTHPA (group SS; presence of serum IgE antibodies against a conjugate of MTHPA and human serum albumin (HSA) detected by RAST had significantly higher levels of tryptase in nasal lavage fluid than 19 non sensitized workers with work-related nasal symptoms (group NS) and 14 non sensitized workers without nasal symptoms (group NN). This suggests an ongoing mast-cell-mediated reaction in the sensitized group.

17-JUL-2002 (21)

Type of experience: Human

Result: One hundred and forty eight workers from two condenser plants (A and B) exposed tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. Ninety seven (66%) of the currently exposed workers had positive MTHPA specific IgE. IgE sensitized workers in each plant had significantly more eye and nose complaints than un-sensitized workers ($p<0.03$). As the result of multiple logistic analysis, specific IgE antibodies was the most important predictor of work-related symptoms and its effect

was greater than that of specific IgG4 (odds ratio 16.7 and 3.68, respectively). These indicate an IgE mediated mechanism in most cases of work-related symptoms associated with MTHPA exposure. However, it cannot be denied IgG4 is an anaphylactic antibody. IgE sensitized workers in these plants displayed work related symptoms despite the presence of specific IgG4. The frequency of positive specific IgG4 in continuously exposed workers was significantly (p<0.02) higher in plant A than in plant B, reflecting the difference of the MTHPA levels between the two plants. In plant A, the frequency of positive specific IgG4 was Significantly (p<0.002) higher in continuously exposed workers than in intermittently exposed workers. These results suggest that work related eye and nasal symptoms are likely to be IgE mediated, and that sepcific IgG4 may reflect the intensity of MTHPA exposure and may not act as a blocking antibody.

07-JUN-2002 (28)

Type of experience: Human

Result: Ninety five workers from two condenser plants (A and B) exposed tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. In all, 24 (65%) of 37 workers in plant A and 38 (66%) of 58 workers in plant B had positive MTHPA-specific IgE. The air levels of MTHPA detected were higher in plant A than plant B (geometric mean 25.5-63.9 and 4.93-5.49 ug/m3, respectively). IgE-sensitized workers in each plant had significantly (P<0.05) more complaints regarding the eyes, nose and pharynx than did those in plat B (P<0.02). The workers in plant A showed stronger and higher frequencies of work related symptoms than workers in plant B. In plant B the minimal level of MTHPA that was associated with work related symptoms was 15-22 ug/m3.

10-MAY-2002 (30)

Type of experience: Human

Result: Twenty five workers and three former workers from two condenser plant exposed tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. Mean MTHPA levels in the manufacturing process to which the workers were routinely assigned were extremely low (1.09-22.4 ug/m3).
However, specific IgE antibody (S-IgE) was detected in 9 (32%) of 28 workers. Of these, 8 (89%) had nasal symptoms. An IgE mediated mechanisms seems to be associated with at least some of the cases of work related nasal symptoms. This indicates that the occupational health administration of MTHPA cannot be controlled simply by limiting exposure in the work environment. Total IgE (T-IgE) levels were significantly higher in S-IgE-positive workers than S-IgE-negative workers. These findings demonstrate that workers in whom S-IgE is less likely to be produced (i.e., those in whom the T-IgE level is 80 IU/ml or less) should be assigned to work in these manufacturing process.

10-MAY-2002 (29)

Type of experience: Human

Result: Seventy three current and 22 former workers underwent a questionnaire survey and serologic investigation. Total and tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) specific IgE levels and MTHPA specific IgG4 levels were measured. Forty-six (63%) of the currently exposed workers had positive MTHPA-specific IgE, and no significant difference was found between those continuously or intermittently exposed (58% and 71%, respectively). The MTHPA levels varied
from 7.47 to 421 ug/m3. The curing ovens leaked 7000 ug MTHPA/m3. Work-related ocular or nasal symptoms were significantly associated with specific IgE but not with specific IgG4. This finding indicates that there is an IgE-mediated mechanism in most case of work-related symptoms associated with MTHPA exposure. The total IgE levels were
significantly (P<0.005) higher in the specific IgE-positive workers than in the specific IgE-negative workers (geometric mean 101 IU/ml and 44.8 IU/ml, respectively). Multiple logistic regression analysis also revealed that the group with high total IgE levels (=>80 IU/ml) had a significant relative risk (RR 4.7) of producing MTHPA-specific IgE as compared with the group with low total IgE levels (<80 IU/ml). These results showed that MTHPA has a high sensitizing ability and that a high total IgE levels is the most significant risk factor for workers exposed to MTHPA.

15-JUL-2002 (32)

Type of experience: Human

Result: A cross sectional survey was carried out on a population of 148 workers from two condenser plants using epoxy resin with
tetrahydromethyl-1,3-isobenzofuranedione (MTHPA). MTHPA-specific IgE was detected from 97 (66%) out of the 148 workers exposed MTHPA. Stepwise multiple liner regression analysis showed a striking relation between log concentration of specific IgE (P<0.0001). Furthermore, when the workers were divided two groups according to a cut-off point (100 IU/ml) between low and high total IgE, current smoking was significantly (P=0.025) associated with specific
IgE production only in the group with low total IgE (<100 IU/ml). So, smoking is the most significant risk
factor for raising specific IgE to MTHPA in the group with low total IgE concentration.

07-JUN-2002 (31)

Type of experience: Human

Result: Two workers contracted hives and itching on uncovered skin after 2 months exposure to
tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) and methyltetrahydrophthalic anhydride (MHHPA), to which they had airbone exposure. On prick testing, both patients also reacted to a phethalic anhydride-hyman serum alubumin conjugate. These patients had developed airbone contact urticaria caused in the unsaturated polyester resin was possibly responsible for the immediate reaction of skin.

17-JUL-2002 (25)

Type of experience: Human

Result: Two hundred and nineteen workers form three plant exposed tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. The exposure assessment included stationaly and ambient air monitoring and biological monitoring (metabolites in urine).
In plant A 20, in plant B 86 and in plant C 113 workers were
examined by a physician. The ambient air concentration of MTHPA were 37.2 and 58.5 ug/m3 in plant A (n=2), ranged from
<0.5-26.2 in plant B (n=5) and from 2.1-57.9 in plant C with
stationaly collecting, and from 8-45 (n=6), from <4.7-35.7 (n=3), and from 2-37.8 (n=3) with personal air collection. The metabolites of MTHPA in urine (in nmol/nmol creatinine) ranged from 5.7-645 in plant A, from <1-213 in plant B and from 0.1-830 in plant C. The prevalence of sensitization was
35% in plant A, 21% in plant B and 29% in plant C. Comparing
the prevalence of sensitization and the results of biological monitoring, between the three plants, it is found
that sensitization increased with increasing exposure. Therefore, biological monitoring is a useful tool in the exposure assessment of MTHPA.

17-JUL-2002 (3)

Type of experience: Human

Result: Six healthy volunteers were exposed to gaseous hexahydrophthalic anhydride (HHPA) concentrations of 10, 40,
or 80 ug/m3 (65, 260, 520 nmole/m3, respectively) for 8 hr. The respiratory uptake of the inhalated HHPA was almost complete. Rapid increases in plasma and urinary levels of hydrophthalic acid (HHP acid) were seen. During the first 4 hr after the end of exposure, the half-time of HHP acid in plasma was about 2 hr. A cressponding decay was seen in urine. The correlations (r>0.90) between the air concentrations of HHPA and levels of HHP acid in plasma and urine were close. They were even closer (r>0.96) when the total respiratory uptake of HHPA was used. Urinary pH adjustment by intake of ammonium chroride or sodium hydrogen
carbonate did not significantry alter the exgretion of HHP acid. The results show that the analysis of HHP acid in plasma or urine is useful as a biological monitor for exposure to HHPA.

17-JUL-2002 (14)

5.11 Additional Remarks

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Appendix 1: Parameters usid in calculation of distribution by Mackey Level III fugacity model (Appendix1 11070443.doc)

Theorotical distribution of 4-methyl-4-cyclohexene-1,2-dicarboxylic acid

scenario 1

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	1,000	1.3.E-08	1.3.E+02	0.0	9.1E+00	1.3.E+00
water	0	4.9.E-02	9.8.E+05	31.6	2.8E+00	9.8.E+02
soil	0	1.3.E+00	2.1.E+06	68.3	6.1E+00	
sediment		5.0.E-02	5.0.E+03	0.2	4.8E-03	9.9.E-02
		totalamount	3.1.E+06			

scenario 2

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	0	8.1.E-14	8.1.E-04	0.0	5.6.E-05	8.1.E-06
water	1000	5.0.E-02	1.0.E+06	99.5	2.9.E+00	1.0.E+03
soil	0	8.2.E-06	1.3.E+01	0.0	3.8.E-05	
sediment		5.1.E-02	5.1.E+03	0.5	4.9.E-03	1.0.E-01
		totalamount	1.0.E+06			

scenario 3

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	0	1.6.E-11	1.6.E-01	0.0	1.1.E-02	1.6.E-03
water	0	4.9.E-02	9.9.E+05	26.9	2.9.E+00	9.9.E+02
soil	1000	1.7.E+00	2.7.E+06	72.9	7.7.E+00	
sediment		5.0.E-02	5.0.E+03	0.1	4.8.E-03	1.0.E-01
		totalamount	3.7.E+06			

scenario 4

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	600	7.9.E-09	7.9.E+01	0.0	5.4.E+00	7.9.E-01
water	300	4.9.E-02	9.9.E+05	39.0	2.8.E+00	9.9.E+02
soil	100	9.6.E-01	1.5.E+06	60.8	4.4.E+00	
sediment		5.0.E-02	5.0.E+03	0.2	4.8.E-03	1.0.E-01
		totalamount	2.5.E+06			

Appendix 1 (Continued)

Physico-chemical parameter

molecular weight		184.19	Calculated
melting point [℃]		124.05	Estimated
vapor pressure [Pa]		1.75E-03	Estimated
water solubility [g/m^3]		10500	Estimated
log Kow		1.28	Estimated
half life [h]	in air	10.04	Estimated
	in water	240000	Estimated
	in soil	240000	Estimated
	in sediment	720000	Estimated

Temp. [℃]	25

Environmental parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon [-]	lipid content [-]	density [kg/m^3]	residence 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

Appendix 2: Genetic toxicity in vitro(1)

Chromosome analysis of Chinese hamster cells (CHL/IU) continuously treated with tetrahydromethyl-1,3-isobenzofurnedion(MTHPA**) without S9mix

Group	Concent-ration (mg/mL)	Time of exopsure (h)	No. of cells analysed	No. of structural aberrations							others[3]
				gap	ctb	cte	csb	cse	mul[2]	total	
Control			200	0	0	0	0	0	0	0	0
Solvent[1]	0	24	200	0	0	0	0	0	0	0	0
MTHPA	0.075	24	200	3	0	0	0	0	0	0	0
MTHPA	0.15	24	200	0	0	0	0	0	0	0	0
MTHPA	0.30	24	200	1	5	12	1	0	20	39	0
MTHPA	0.60***	24	-								
MC	0.00005	24	200	4	44	113	4	1	0	166	0
Solvent[1]	0	48	200	1	0	0	1	0	0	2	0
MTHPA	0.075	48	200	2	1	0	0	0	0	3	0
MTHPA	0.15	48	200	0	0	1	0	0	0	1	0
MTHPA	0.30	48	200	0	6	2	1	2	0	11	3
MTHPA	0.60***	48	-								
MC	0.00005	48	200	3	85	152	10	7	10	267	10

continue

Group	Concent-ration (mg/mL)	Time of exopsure (h)	No. of cells with aberrations		Polyploid[4]	Trend test[5]		Concurrent cytotoxicity[6]
			TAG(%)	TA(%)	(%)	SA	NA	(%)
Control			0(0.0)	0(0.0)	0.25			-
Solvent[1]	0	24	0(0.0)	0(0.0)	0.00			100.0
MTHPA	0.075	24	3(1.5)	0(0.0)	0.25			103.5
MTHPA	0.15	24	0(0.0)	0(0.0)	0.00	+	NT	104.5
MTHPA	0.30	24	8*(4.0)	7(3.5)	0.50			71.0
MTHPA	0.60***	24			-			0.0
MC	0.00005	24	97(48.5)	95(47.5)	0.38			-
Solvent[1]	0	48	2(1.0)	1(0.5)	0.25			100.0
MTHPA	0.075	48	3(1.5)	1(0.5)	0.13			97.0
MTHPA	0.15	48	1(0.5)	1(0.5)	0.25	NT	+	99.5
MTHPA	0.30	48	6(3.0)	6(3.0)	1.13*			71.5
MTHPA	0.60***	48						0.0
MC	0.00005	48	109(54.5)	108(54.0)	0.88			-

Abbreviations, gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, csb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total number of cells with aberrations, TA: total number of cells with aberrations except gap, SA: structural aberration, NA: numerical aberration, MC: mitomycin C, NT: not tested, 1)Dimethylsulfoxide was used as solvent. 2)More than nine aberrations in a cell were scored as 10. 3)Others, such as attenuation and premature chromosome condensation, were excluded from the number of structural aberrations. 4)Eight hundred cells were analyzed in each group. 5)Cochran-Armitage's trend test was done at $p<0.05$. 6)Cell confluency, representing cytotoxicity, was measured with Monocellater™ *:Significantly different from historical solvent control data at $p<0.05$ by Fisher's exact test using a Bonferroni correction for multiple comparisons. **:Test substance was prescribed at page 2. ***:Chromosome analysis was performed because of severe cytotoxicity.

(continued)

Genetic toxicity in vitro(2)

Chromosome analysis of Chinese hamster cells (CHL/IU) treated with tetrahydromethyl-1,3-isobenzofurnedion(MTHPA**) with and without S9mix

Group	Concent-ration (mg/mL)	S9 mix	Time of exopsure (h)	No. of cells analysed	No. of structural aberrations							others[3]
					gap	ctb	cte	csb	cse	mul[2]	total	
Control				200	0	0	1	3	0	0	4	1
Solvent[1]	0	-	6(-18)	200	0	1	0	0	0	0	1	0
MTHPA	0.050	-	6(-18)	200	0	0	0	0	0	0	0	0
MTHPA	0.10	-	6(-18)	200	0	0	0	0	0	0	0	0
MTHPA	0.20	-	6(-18)	200	0	0	0	0	0	0	0	0
MTHPA	0.40***	-	6(-18)	-								
MTHPA	0.80***	-	6(-18)	-								
CPA	0.005	-	6(-18)	200	2	0	1	0	0	0	3	0
Solvent[1]	0	+	6(-18)	200	3	0	0	0	0	0	3	0
MTHPA	0.11	+	6(-18)	200	0	1	0	0	0	0	1	0
MTHPA	0.21	+	6(-18)	200	0	1	0	0	0	0	1	0
MTHPA	0.43	+	6(-18)	200	0	1	3	0	0	0	4	0
MTHPA	0.85***	+	6(-18)	-								
MTHPA	1.7***	+	6(-18)	-								
CPA	0.005	+	6(-18)	200	12	140	283	2	2	50	489	0

continue

Group	Concent-ration (mg/mL)	S9 mix	Time of exopsure (h)	No. of cells with aberrations		Polyploid[4]	Trend test[5]		Concurrent cytotoxicity[6]
				TAG(%)	TA(%)	(%)	SA	NA	(%)
Control				2(1.0)	2(1.0)	0.38			-
Solvent[1]	0	-	6(-18)	1(0.5)	1(0.5)	0.25			100.0
MTHPA	0.050	-	6(-18)	0(0.0)	0(0.0)	0.50			103.0
MTHPA	0.10	-	6(-18)	0(0.0)	0(0.0)	0.38	NT	NT	106.0
MTHPA	0.20	-	6(-18)	0(0.0)	0(0.0)	0.38			36.0
MTHPA	0.40***	-	6(-18)						1.5
MTHPA	0.80***	-	6(-18)						0.0
CPA	0.005	-	6(-18)	3(1.5)	1(0.5)	0.25			-
Solvent[1]	0	+	6(-18)	3(1.5)	0(0.0)	0.13			100.0
MTHPA	0.11	+	6(-18)	1(0.5)	1(0.5)	1.25			97.0
MTHPA	0.21	+	6(-18)	1(0.5)	1(0.5)	1.50			99.5
MTHPA	0.43	+	6(-18)	2(1.0)	2(1.0)	1.88	NT	+	71.5
MTHPA	0.85***	+	6(-18)						0.0
MTHPA	1.7***	+	6(-18)						
CPA	0.005	+	6(-18)	157(78.5)	155(77.5)	0.50			-

Abbreviations, gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, csb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total number of cells with aberrations, TA: total number of cells with aberrations except gap, SA: structural aberration, NA: numerical aberration, MC: mitomycin C, NT: not tested, 1)Dimethylsulfoxide was used as solvent. 2)More than nine aberrations in a cell were scored as 10. 3)Others, such as attenuation and premature chromosome condensation, were excluded from the number of structural aberrations. 4)Eight hundred cells were analyzed in each group. 5)Cochran-Armitage's trend test was done at $p<0.05$. 6)Cell confluency, representing cytotoxicity, was measured with Monocellater™ *:Significantly different from historical solvent control data at $p<0.05$ by Fisher's exact test using a Bonferroni correction for multiple comparisons. **:Test substance was prescribed at page 2. ***:Chromosome analysis was not performed because there were small number of methaohases due to severe cytotoxicity