

**FOREWORD**

**INTRODUCTION**

**TETRAHYDROMETHYL-1,3-ISOBENZOFURANEDIONE**

CAS N°: 11070-44-3

## SIDS Initial Assessment Report

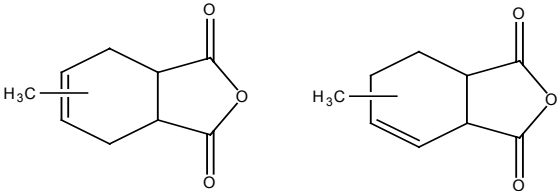
For

### 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. Katsuro 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**

<b>CAS No.</b>	11070-44-3
<b>Chemical Name</b>	Tetrahydromethyl-1,3-isobenzofuranedione
<b>Structural Formula</b>	
<b>SUMMARY CONCLUSIONS OF THE SIAR</b>	
<p>This chemical is a mixture of several chemical species as defined by the above described structure.</p>	
<b>Human Health</b>	
<p>There is no available information on metabolism or toxicokinetics of this substance in animals. This chemical is, nevertheless, known to be metabolized to di-carboxylic acid and excreted in urine in human, when inhaled. <math>T_{1/2}</math> for the excretion is estimated as ca. 3-6 hr.</p>	
<p>In acute oral toxicity studies [OECD TG 401] in rats, the <math>LD_{50}</math> 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.</p>	
<p>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.</p>	
<p>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.</p>	
<p>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.</p>	
<p>Bacterial genotoxicity studies showed negative results in <i>S. typhimurium</i> and <i>E. coli</i> 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.</p>	
<b>Environment</b>	
<p>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</p>	

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<sub>50</sub> (immobility in *Daphnia magna*, 48 hr). The toxicity to fish (Medaka) [OECD TG 203] was more than 100 mg/l for LC<sub>50</sub> (96 hr). The prolonged toxicity to fish (Medaka)[OECD TG 204] was more than 100 mg/l for LC<sub>50</sub> (14 d).

The toxicities of tetrahydromethyl-1,3-isobenzofuranedione to algae [OECD TG 201, *Selenastrum capricornutum*] were 55 mg/l for ErC<sub>50</sub> (growth rate 24-48 h) and 64 mg/l for EbC<sub>50</sub> (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<sub>50</sub> (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 hydrolysis 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<sup>3</sup> 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								
<b>PHYSICAL-CHEMICAL</b>												
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 <sup>3</sup>								
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								
<b>ENVIRONMENTAL FATE AND PATHWAY</b>												
3.1.1	Photodegradation		Calculated	T <sub>1/2</sub> = 2.979 hrs								
			[Calculated on 4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysates of this substance)]	[T <sub>1/2</sub> = 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)	(Release 100% to air)								
			4-methyl-4-cyclohexene-1,2-dicarboxylic acid (one of the hydrolysates of this substance) (local exposure)	<table border="1"> <tr> <td>Air</td> <td>Water</td> <td>Soil</td> <td>Sediment</td> </tr> <tr> <td>0.0%</td> <td>31.6%</td> <td>68.3%</td> <td>0.2%</td> </tr> </table>	Air	Water	Soil	Sediment	0.0%	31.6%	68.3%	0.2%
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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								
<b>ECOTOXICOLOGY</b>												
4.1	Acute/Prolonged Toxicity to Fish	<i>Oryzias latipes</i>	OECD TG 203	LC <sub>50</sub> (96 hr) > 100 mg/L :flow through								
			OECD TG 204	LC <sub>50</sub> (14 d) > 86 mg/L :flow through								
4.2	Acute Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (48hr,Imm) = 130 mg/L :static								
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD TG 201	EC <sub>50</sub> (72hr,Bms) = 64 mg/L NOEC(72hr,Bms) = 27.5mg/L EC <sub>50</sub> (24-48hr,gr) = 55 mg/L NOEC(24-72hr,gr) =27.5 mg/L :static								

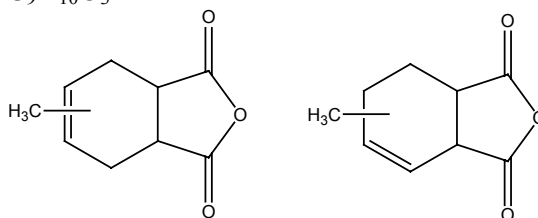
4.5.2	Chronic Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (21d,Rep)= 9.2 mg/L NOEC(21d,Rep)= 0.94 mg/L :semi static
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			
<b>TOXICOLOGY</b>				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD <sub>50</sub> > 2000 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Other	LD <sub>50</sub> = 1900 mg/kg 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 <i>in vitro</i>			
A.	Bacterial Test (Gene mutation)	<i>S.typhimurium</i> <i>E. coli</i>	OECD TG 471 & 472	Negative
B.	Non-Bacterial <i>in vitro</i> Test (Chromosomal aberrations)	CHL cell	OECD TG 473	Equivocal
5.6	Genetic Toxicity <i>in vivo</i> (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/cm <sup>3</sup> 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.

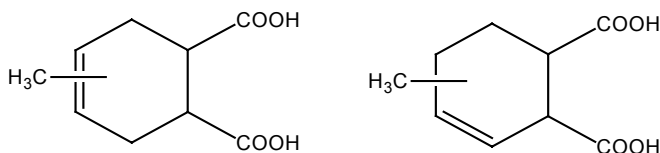
This substance is not usually released to the environment from the production and use site, except during sampling and maintenance.

### 2.2 Environmental Exposure and Fate

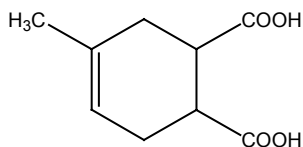
#### 2.2.1 Sources of Environmental Exposure

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**



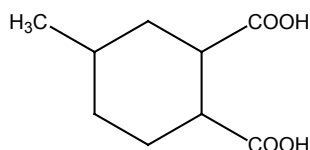
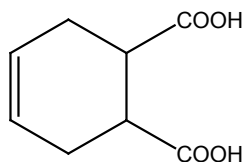
**Fig. 2: Structural formula of 4-methyl-4-cyclohexene-1, 2-dicarboxylic acid**

**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 <sup>3</sup> )		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<sup>3</sup> at sampling work.

**Table 4:** Occupational exposure levels at processing sites

Occupation (country)	Process	Monitoring data (ug/m <sup>3</sup> )		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	20-150 and 5-20 *	-	Nielsen, J. et al. (1992)
	and curing	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<sup>3</sup>/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<sup>3</sup> (Yokota, K. et al. 1998a).

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

The Japan Society for Occupational Health recommended 50  $\mu\text{g}/\text{m}^3$  (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<sub>50</sub> 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<sub>50</sub> value was 1900 mg/kg.

In summary, based on the two studies described above, oral LD<sub>50</sub> 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
<i>Oral</i>					
	Rat	>2000 mg/kg(both sex)	LD <sub>50</sub>	Y	MHW Japan (1997a)
	Rat	1900mg/kg(both sex)	LD <sub>50</sub>	Y	Huntingdon Research Center (1980a)
	Rat	2102mg/kg(both sex)	LD <sub>50</sub>	N	Hitachi Chemical (1969)
	Mouse	1707 mg/kg(male)	LD <sub>50</sub>	N	Hitachi Chemical (1969)
	Rat	2140 mg/kg(not cited)	LD <sub>50</sub>	unknown	Lonza SpA (2000)
	Rat	2.14 ml/kg*(not cited)	LD <sub>50</sub>	unknown	H. F. Smyth et.al. (1969)#
<i>Intra peritoneal</i>					
	Rat	255 mg/kg(male)	LD <sub>50</sub>	N	Hitachi Chemical (1969)
	Mouse	222 mg/kg(male)	LD <sub>50</sub>	N	Hitachi Chemical (1969)
<i>Dermal</i>					
	Rabbit	1.41 ml/kg*(not cited)	LD <sub>50</sub>	unknown	H. F. Smyth et.al. (1969)#
	Rat	>2000 mg/kg*(not cited)	LD <sub>50</sub>	Y	Lonza SpA (2000) \$

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

#: Review article

\$: Secondary information

### Studies in Humans

This substance (TWA of this substance ca. 20-150 µg/m<sup>3</sup>) 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<sub>50</sub>: 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 corneal 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<sup>3</sup> 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
<i>Bacterial test</i>					
Ames test (reverse mutation)	<i>S.typhimurium</i> (strains TA98, TA100, TA1535, TA1537) <i>E.coli</i> WP2uvrA OECD TG 471 & 472	Up to 5 mg/plate	with	Negative	MHW, Japan (1997c)
		Up to 2 mg/plate	without	Negative	
<i>Non-bacterial invitro test</i>					
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 uvrA. 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 be 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
<i>Aquatic plants</i>			
Green algae ( <i>Selenastrum capricornutum</i> ) ATCC 22662	OECD TG 201 72 hr (cl, s)	EC <sub>50</sub> (72 hr, bms) = 64(mc) EC <sub>50</sub> (24-48 hr, gr) = 55(mc) NOEC(72 hr, bms) = 27.5(mc) NOEC(24-72 hr, gr) = 27.5(mc)	MOE, Japan (1997a)
<i>Invertebrates</i>			
Water flea ( <i>Daphnia magna</i> )	OECD TG 202 24, 48 hr (op, s)	EC <sub>50</sub> (24 hr, imm) = 180(mc) EC <sub>50</sub> (48 hr, imm) = 130(mc)	MOE, Japan (1997b)
	OECD TG 202 21 d (op, ss)	LC <sub>50</sub> (21 d) > 110(mc) EC <sub>50</sub> (21 d, rep) = 9.2(mc) NOEC(21 d, rep) = 0.94(mc) LOEC(21 d, rep) = 3.5(mc)	MOE, Japan (1997c)
<i>Fish</i>			
Medaka ( <i>Oryzias latipes</i> )	OECD TG 203 96 hr (op, f)	LC <sub>50</sub> (96 hr) > 100(nc*)	MOE, Japan (1997d)
	OECD TG 204 14 d (op, f)	LC <sub>50</sub> (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<sub>50</sub> (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<sub>50</sub> (48 hr) value for immobility to *Daphnia magna* [OECD TG 202 part 2] was 130 mg/l and the EC<sub>50</sub> (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<sub>50</sub> 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<sub>50</sub> (immobility in *Daphnia magna*, 48 hr). The toxicity to fish (Medaka) [OECD TG 203] was more than 100 mg/l for LC<sub>50</sub> (96 hr). The prolonged toxicity to fish (Medaka)[OECD TG 204] was more than 100 mg/l for LC<sub>50</sub> (14 d).

The toxicities of tetrahydromethyl-1,3-isobenzofuranedione to algae [OECD TG 201, *Selenastrum capricornutum*] were 55 mg/l for ErC<sub>50</sub> (growth rate 24-48 h) and 64 mg/l for EbC<sub>50</sub> (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<sub>50</sub> (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

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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. GENERAL INFORMATION

ID: 11070-44-3

DATE: 13.5.2004

## 1.0.1 Applicant and Company Information

Type: lead organisation  
Name: Hitachi Chemical Co., Ltd.  
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26-AUG-2002

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Homepage: http://www.zeon.co.jp/

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

## 1. GENERAL INFORMATION

ID: 11070-44-3

DATE: 13.5.2004

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 tetrahydrophthalic acid  
Mol. Formula: C9H12O4  
Contents: ca. .01 - % w/w

## 1. GENERAL INFORMATION

ID: 11070-44-3

DATE: 13.5.2004

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 tons/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

## 1. GENERAL INFORMATION

ID: 11070-44-3

DATE: 13.5.2004

---

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:Recommendation 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 m<sup>3</sup>/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. Workers recognize the fact that this substance has irritating activity to skin and they are recommended to wear protective equipment (mask, 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/m<sup>3</sup> (maximum concentration at assembly process in Japanese plant), body weight; 70 kg, respiratory volume 1.25 m<sup>3</sup>/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. PHYSICO-CHEMICAL DATA

ID: 11070-44-3

DATE: 13.5.2004

## 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

## 2. PHYSICO-CHEMICAL DATA

ID: 11070-44-3

DATE: 13.5.2004

---

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/cm<sup>3</sup> 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 soluble 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 prescribed 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



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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

## 3.1.1.1 Photodegradation

Type: air  
Light source: Sun light  
Conc. of subst.: at 25 degree C

## INDIRECT PHOTOLYSIS

Sensitizer: OH  
Conc. of sens.: 1.5 molecule/cm<sup>3</sup>

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

Method: Calculated by using AOPWIN (v1.90)  
Result: Rate constant: 43.0843X10 E-12cm<sup>3</sup>/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/cm<sup>3</sup>

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

Method: Calculated by using AOPWIN (v1.90)  
Result: Rate constant: 12.784X10 E-12cm<sup>3</sup>/molecule-sec  
Rate constant: 43.0843X10 E-12cm<sup>3</sup>/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                    Release                    Release  
                   100% to air    100% to water    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

## 3. ENVIRONMENTAL FATE AND PATHWAYS

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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: Calculated 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 (CuSO<sub>4</sub> 5H<sub>2</sub>O) = 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 CaCO<sub>3</sub>  
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 apparently 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 substance 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
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

-LC50:  
Exposure time 7days LC50 > 86 mg/l  
14days LC50 > 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 concentration (mg/l)	Measured concentration(mg/l) (percentage of nominal)			Mean*
	0-hr	48-hr		

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	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:

Test condition:

MOE Japan 1997

-Test Organisms:

- Age at Study Initiation: <24 hr after hatching
- Supplier/Source: Supplied from Sumika Tecnoservice Co.
- Sensitivity to reference substance:  
48 hr EC50 of reference substance (K2CrO4) = 0.80 mg/l

-Test Condition:

- Dilution Water Source: dechlorinated tap water
- Dilution Water Chemistry:  
hardness = 62 mg/l as CaCO3  
pH = 7.9,  
chlorine concentration <0.01 mg/l
- Exposure Vessel Type: 100 ml glass beaker
- Nominal Concentration (as mg/l): 32, 56, 100, 180 and 320  
(Nominal concentration << water solubility (>1000 mg/l))
- Vehicle/Solvent and Concentrations:  
Solvent; Not used
- Stock Solutions Preparations and Stability:  
Tetrahydromethyl-1,3-isobenzofurandione added in dechlorinated tap water (1000 mg/l) and stirred more than 60 min.
- Number of Replicates: 4
- Individuals per Replicates: 5
- Renewal Rate of Test Water: water renewal; No
- Water temperature: 19-21°C degrees C
- Intensity of Irradiation: room light

1) 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°C 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 Cell density (x 10E+4 cells/ml)  
 (mg/l) 0-hr 24-hr 48-hr 72-hr

	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:  
 Test condition:

MOE Japan 1997  
 -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:  $IA = (Ac - At) \times 100 / Ac$   
 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.  
 Critical study for SIDS endpoint

Flag:  
 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)				Time Weighted Mean
	9day new*	12day old#	16day old#	19day old#	
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 REFERENCE 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)

Source: LD50: Male: >2000 mg/kg ; Female : >2000 mg/kg  
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, Huntingdon,  
 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 Addititives 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 (mg/kg/day)	0	30	100	300
Body weight (g, Mean+/-SD)	516.5 +/-30.2	530.4 +/-18.6	530.9 +/-27.4	492.8 +/-35.0
Absolute weight				
Kidney (g, Mean+/-SD)	2.99 +/-0.21	3.00 +/-0.09	3.17 +/-0.24*	3.05 +/-0.27
Adrenal (mg, Mean+/-SD)	53.2 +/-6.2	57.3 +/-4.7	60.8 +/-5.9*	60.3 +/-13.4
Relative weight				
Adrenal (mg%, Mean+/-SD)	10.3 +/-0.9	10.8 +/-1.1	11.3 +/-1.2	12.2 +/-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 animals	12			
Organs and findings	-	+	++	+++
Forestomach				
Squamous hyperplasia	11	1	0	0

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,	0	0	0	0	0	1	0	0	0	1	0	0
mucosa layer												
Cellular infiltration,												
mucosal layer												
Lung												
Fatty	11	0	0	0	0	1	0	0	11	1	0	0
droplet, alveoli												
Thymus												
Atrophy	10	1	0	0	0	1	0	0	10	2	0	0
Kidney												
Necrosis,	11	0	0	0	0	1	0	0	11	1	0	0
tubular epithelium,												
cortex, Cloacal												
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 kidney(s) weight increase was observed in male 100 and/or 300 mg/kg group, but there is no histopathological change was observed, so we the author exclude this observation. Squamous hyperplasia was observed in only one male of 100 mg/kg group, so we the author exclude this observation. Therefore, we decided the NOAEL as 100 mg/kg in male.

Source:  
Test condition:

MHW, Japan  
-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 groups; 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: continuous 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: Japanese 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

Source: Detail is shown in APPENDIX 2\_11070443.doc  
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

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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 (Mean+/-SD)	183 16.64 +/-1.63	188 17.09 +/-1.30	188 17.09 +/-0.94	162 16.20 +/-1.03
No. of litter (Mean+/-SD)	171 15.55 +/-2.58	178 16.18 +/-1.25	181 16.45 +/-0.69	154 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 (Mean+/-SD)	162 14.73 +/-2.65	150 13.64 +/-1.43	160 14.55 +/-0.82	138 13.80 +/-2.53
Birth index	94.74	84.27*	88.40*	89.61
Sex ratio of live newborns (male/female)	0.98 (80/82)	0.90 (71/79)	1.08 (83/77)	0.86 (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 methyltetrahydrophthalic 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-methyl-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 trifluoride. 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/m<sup>3</sup>. 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 m<sup>3</sup> 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.  
(2) valid with restrictions  
Critical study for SIDS endpoint  
Reliability:  
Flag:  
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 rhinitis 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/m<sup>3</sup>. 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/m<sup>3</sup>, in zone II 14 ug/m<sup>3</sup>, and in zone III 10ug/m<sup>3</sup>. 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 were statistically significant exposure-response relations between exposure and symptoms.

18-JUL-2002 (22)

Type of experience: Human

Result: Forty 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 specific 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  $\mu\text{g}/\text{m}^3$ , respectively). IgE-sensitized workers in each plant had significantly ( $P < 0.05$ ) more complaints regarding the eyes, nose and pharynx than did those in plant 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  $\mu\text{g}/\text{m}^3$ .

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  $\mu\text{g}/\text{m}^3$ ). 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 ( $\geq 80$  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 airborne exposure. On prick testing, both patients also reacted to a phethalic anhydride-human serum albumin conjugate. These patients had developed airborne 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 from three plants exposed to tetrahydromethyl-1,3-isobenzofuranedione (MTHPA) used as a hardener in an epoxy resin system were reported. The exposure assessment included stationary 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/m<sup>3</sup> 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 stationary 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/m<sup>3</sup> (65, 260, 520 nmole/m<sup>3</sup>, respectively) for 8 hr. The respiratory uptake of the inhaled 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 corresponding 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 chloride or sodium hydrogen carbonate did not significantly alter the excretion 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 used in calculation of distribution by Mackey Level III fugacity model  
(Appendix1 11070443.doc)

**Theoretical distribution of 4-methyl-4-cyclohexene-1,2-dicarboxylic acid**

scenario 1

	emission rate [kg/h]	conc. [g/m <sup>3</sup> ]	amount [kg]	percent [%]	transformation 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
		total amount	3.1.E+06			

scenario 2

	emission rate [kg/h]	conc. [g/m <sup>3</sup> ]	amount [kg]	percent [%]	transformation 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
		total amount	1.0.E+06			

scenario 3

	emission rate [kg/h]	conc. [g/m <sup>3</sup> ]	amount [kg]	percent [%]	transformation 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
		total amount	3.7.E+06			

scenario 4

	emission rate [kg/h]	conc. [g/m <sup>3</sup> ]	amount [kg]	percent [%]	transformation 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
		total amount	2.5.E+06			

Appendix 1 (Continued)

Physico-chemical parameter

molecular weight	184.19	Calculated	
melting point [°C]	124.05	Estimated	
vapor pressure [Pa]	1.75E-03	Estimated	
water solubility [g/m <sup>3</sup> ]	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. [°C]	25
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Environmental parameter

		volume [m <sup>3</sup> ]	depth [m]	area [m <sup>2</sup> ]	organic carbon [-]	lipid content [-]	density [kg/m <sup>3</sup> ]	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				

Intermediate 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-isobenzofurandion(MTHPA\*\*) without S9mix

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

*continue*

Group	Concentration (mg/mL)	Time of exposure (h)	No. of cells with aberrations		Polyploid <sup>4)</sup> (%)	Trend test <sup>5)</sup>		Concurrent cytotoxicity <sup>6)</sup> (%)
			TAG(%)	TA(%)		SA	NA	
Control			0(0.0)	0(0.0)	0.25			-
Solvent <sup>1)</sup>	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 <sup>1)</sup>	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<sup>TM</sup> \*: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-isobenzofurandion(MTHPA\*\*) with and without S9mix

Group	Concentration (mg/mL)	S9 mix	Time of exposure (h)	No. of cells analysed	No. of structural aberrations							total	others <sup>3)</sup>
					gap	ctb	cte	csb	cse	mul <sup>2)</sup>			
Control				200	0	0	1	3	0	0	4	1	
Solvent <sup>1)</sup>	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 <sup>1)</sup>	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	Concentration (mg/mL)	S9 mix	Time of exposure (h)	No. of cells with aberrations		Polyploid <sup>4)</sup> Trend test <sup>5)</sup>		Concurrent cytotoxicity <sup>6)</sup>	
				TAG(%)	TA(%)	(%)	SA	NA	(%)
Control				2(1.0)	2(1.0)	0.38			-
Solvent <sup>1)</sup>	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 <sup>1)</sup>	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<sup>TM</sup> \*.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