FOREWORD INTRODUCTION

2-DIMETHYLAMINOETHYLMETHACRYLATE

CAS N°: 2867-47-2

SIDS Initial Assessment Report for SIAM 14

(Paris, 26-28 March 2002)

Chemical Name: 2-Dimethylaminoethyl methacrylate

CAS No: 2867-47-2

Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:
Mr. Koji Tomita
Ministry of Foreign Affairs, Economic Affairs Bureau, Second International Organizations Division.

Industry: Mr. Kazuhiro Sugamura
Mitsubishi Gas Chemical Company, Inc.
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History: This substance was sponsored by Japan under the ICCA Initiative and was submitted for first discussion at SIAM 14.

Peer Review Process:
The industry consortium 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.

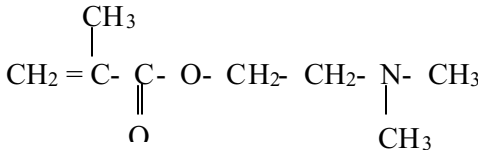
Testing: No testing (X) Testing ( )

Comments: The industry contact point is Mr. Kazuhiro Sugamura, Mitsubishi Gas Chemical Company, Inc. acting on behalf of MADAME (2-Dimethylaminoethyl methacrylate) Consortium (Consortium members: Atofina, Ciba Specialty Chemicals Inc., Degussa / Roehm GmbH & Co., Mitsubishi Rayon Co., Ltd., Mitsui Chemicals, Inc., Sanyo Chemical Industries, Ltd., SNF S.A.).

Deadline for circulation: 1 Feb. 2002

Date of circulation: 1 Feb. 2002

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2867-47-2
Chemical Name	2-Dimethylaminoethyl methacrylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2-Dimethylaminoethyl methacrylate is supposedly metabolized to methacrylic acid and N,N-dimethylaminoethanol. Then the methacrylic acid may form an acetyl-CoA derivative, which then enters the normal lipid metabolism. The oral LD_{50} in rats is greater than 2000 mg/kg. This chemical is considered to be severely irritating or corrosive to skin and eye. This chemical does not have a sensitizing potential.

The OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422] was conducted in rats at doses of 0, 40, 200 and 1000 mg/kg/day administered by gavage. For both sexes, a clear systemic toxicity was demonstrated only at 1000 mg/kg/day. Late onset of twitching, chronic convulsion and the suppression of body weight gain were observed. Three females out of 12 died. Histopathological examination revealed degeneration of nerve fibers in the brain and spinal cord, and hyperplasia of the mucosa, edema and inflammatory cell infiltration in the forestomach in both sexes. Increases in organ weights without histopathological changes were observed in the kidneys of both sexes, the livers of males, and the adrenals of females in this group. For the males in this group, BUN was slightly increased and anemic changes such as decreases in erythrocyte counts, hemoglobin concentration and hematocrit value, associated with a significant increase in reticulocyte ratio were observed. In males from the 200 mg/kg/day group, only slight anemic changes such as those observed at 1,000 mg/kg/day were seen, but the severity was considered toxicologically insignificant. The NOAEL for the repeat dose toxicity is considered to be 200 mg/kg/day.

A repeated inhalation study for 3 weeks revealed a NOEL of 100 ppm. Nose and eye irritation was observed at 250 ppm (LOEL).

Two independent gene mutation tests in bacteria [OECD TG 471 & 472] resulted in negative results except for a positive result in *S. typhimurium* TA 1537 at 2500 ug without metabolic activation in one study. A HPRT study on Chinese hamster cultured cells [OECD TG 476] was negative. A chromosomal aberration test *in vitro* [TG 473] and a human lymphocyte test were positive with and without metabolic activation.
However two *in vivo* studies [micronucleus assay, OECD TG 474] by i.p. or gavage respectively, gave

negative results. Based on the weight of evidence, it is concluded that this chemical is not genotoxic *in vivo*.

In the above-described OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], there was no sign of reproductive toxicity up to 1000 mg/kg/day for males. Three females in the 1,000 mg/kg/day group, however, lost all of their pups in the lactation period. As to the developmental effect, the pups born from the females in the 1000 mg/kg/day group showed a lower body weight although no external abnormalities were observed. The NOAEL of the reproductive/developmental toxicity is considered to be 200 mg/kg/day for both parents and offspring.

Environment

Abiotically 2-dimethylaminoethyl methacrylate is hydrolyzed at pH7 and at pH 9 with a half-life of 4.54 days and 3.31 hours, respectively, whereas it is stable at pH 4. This chemical is readily biodegradable ([OECD TG 301E]; BOD: 95.3 % after 28 days), and has low bioaccumulation potential based on its log Kow of 1.13.

This chemical has been tested in a limited number of aquatic species including algae, daphnids and fish. The toxicity results (growth inhibition: [OECD TG 201]) for algae (*Selenastrum capricornutum*) were 41.6 mg/L (72 h-EC_{50}) and 18 mg/L (72 h-NOEC). The acute (immobility: [OECD TG 202]) and chronic (reproduction: [OECD TG 211]) toxicity results for daphnids are 33 mg/L (48h-EC_{50}), 16.6 mg/L (21d-LC_{50}), 7.86 mg/L (21d-EC_{50}), and 4.35 mg/L (21d-NOEC), respectively. The acute LC_{50} (96 hr: [OECD TG 203]) and prolonged LC_{50} (14 d: [OECD TG 204]) for fish (Medaka; *Oryzias latipes*) were 19.1 mg/L and 5.26 mg/L, respectively. Although 2-dimethylaminoethyl methacrylate can be hydrolyzed in these test conditions to methacrylic acid and dimethylaminoethanol, these results are, however, consistent with the aquatic toxicity of the metabolites reported in the respective SIARs issued in the past.

Exposure

The production volume of 2-dimethylaminoethyl methacrylate was estimated at approximately 8,000 t/year in Japan and 48,000 t/year world-wide in 2000. 2-Dimethylaminoethyl methacrylate is produced in a fully-closed system. Most of 2-dimethylaminoethyl methacrylate is industrially converted to the quaternary ammonium salt and polymerized for flocculant use in water treatment. This chemical is also used as a component monomer of copolymers in the polymer industry, and the products are used for paper agents, coatings and others. The workplace exposures during those application processes are controlled. Fugacity modeling (Mackay level III) predicts that 2-dimethylaminoethyl methacrylate released to water unlikely will migrate into other compartments. 2-Dimethylaminoethyl methacrylate is readily biodegradable and not persistent in the water phase. When this chemical is released to air, 72 % stays in air and 28 % is transported into water and soil.

During production and use of this substance occupational exposure is possible by inhalation of vapor. Consumer exposure is controlled because it is limited to the non-dispersive use.

Migration of residual monomer from the polymer matrix is expected to be low. Nevertheless, the possibility of exposure cannot be excluded.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is not a candidate for further work considering the low bioaccumulation potential, ready biodegradability and low aquatic toxicity.

FULL SIDS SUMMARY

CAS NO: 2867-47-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	- 30 °C
2.2	Boiling Point		Unknown	186 °C
2.3	Density		Unknown	0.934 g/cm^3 at 20 °C
2.4	Vapour Pressure		Calculated	1.10 hPa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	1.13 at 25 °C
2.6 A.	Water Solubility		Unknown	106.1 g/L at 25 °C
B.	pH			No data available
	pKa		OECD 112	8.44 at 25 °C
2.12	Oxidation: Reduction Potential			No data available
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated	$T_{1/2}$ = 4 hrs
3.1.2	Stability in Water		OECD TG 111	Stable at pH4 at 50 °C $T_{1/2}$ = 4.54 days at pH7 at 25 °C $T_{1/2}$ = 3.31 hrs at pH9 at 25 °C
3.2	Monitoring Data			No study
3.3	Transport and Distribution		Calculated (Level III Fugacity Model)	(Release 100% to air) Air Water Soil Sediment 72.1% 13.6% 14.2% 0.0% (Release 100% to water) Air Water Soil Sediment 0.0% 99.7% 0.0% 0.2% (Release 100% to soil) Air Water Soil Sediment 0.1% 5.7% 94.2% 0.0%
3.5	Biodegradation		OECD 301E	Readily biodegradable BOD: 95.3% after 28days
3.7	Bioaccumulation			No data available
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50}(96hr) = 19.1 mg/L
			OECD TG 204	LC_{50}(14d) =5.26 mg/L LC_0 (14d) = 1.36 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(48hr,Imm) = 33 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50}(72hr,Bms) = 41.6 mg/L NOEC(72hr,Bms) =18 mg/L
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 211	EC_{50}(21d,Rep)= 7.86 mg/L NOEC(21d,Rep)= 4.35 mg/L
4.6.1	Toxicity to Soil Dwelling Organisms			No data available
4.6.2	Toxicity to Terrestrial Plants			No data available
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			

TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} > 2000 mg/kg
5.1.2	Acute Inhalation	Mouse	Other	LC_{50} (2 h) = 1.8 mg/L (280 ppm)
	Toxicity	Rat	Other	LC_{50} (4 h) = 0.62 mg/L
5.1.3	Acute Dermal Toxicity	Rat	Other	LD_{50} > 2000 mg/kg
		Rabbit		LD_{50} > 3000 mg/kg
5.2.1	Skin Irritation	Rabbit	Other	irritating
5.2.2	Eye Irritation	Rabbit	Other	Corrosive
5.3	Skin Sensitisation	Guinea pig	OECD TG 406	Not sensitizing
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	NOAEL = 200 mg/kg/day (both sexes)
5.5	Genetic Toxicity *in vitro*			
A.	Bacterial Test (Gene mutation)	*S.typhimurium* *E. coli*	OECD TG 471 & 472	Positive (for only TA 1537)
		S.typhimurium	OECD TG 471	Negative
B.	Non-Bacterial *in vitro* Test (Chromosomal aberrations)	CHL cell	OECD TG 473	Positive
	Non-Bacterial *in vitro* Test (Chromosomal aberrations)	Human lympocytes	Other	Positive
	HPRT Assay	V79 Chinese Hamster cell	OECD TG 476	Negative
5.6	Genetic Toxicity *in vivo* (Micronucleus Test)	Mouse (p.o)	OECD TG 474	Negative
		Mouse (i. p)	OECD TG 474	Negative
5.7	Carcinogenicity			No data available
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL Reproductive/Developmental= 200 mg/kg/day.
5.9	Developmental Toxicity/ Teratogenicity			No teratogenicity
5.11	Experience with Human Exposure			No data available

SIDS INITIAL ASSESSMENT REPORT (SIAR)

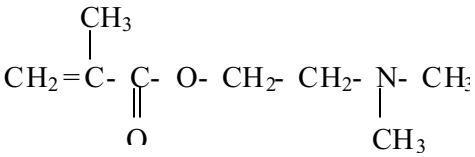
1. IDENTITY

IUPAC name: 2-Dimethylaminoethyl methacrylate

CAS Number: 2867-47-2

Molecular Formula: $C_8H_{15}NO_2$

Structural Formula:



Synonyms:

MADAME
DAM
2-(Dimethylamino) ethanolmethacrylate
2-(N, N-Dimethylamino) ethylmethacrylate
2-Dimethylaminoethyl methacrylate
2-Dimethylaminoethyl-2-methyl-propenoate
N, N-Dimethylaminoethyl methacrylate
beta- (N, N-Dimethylaminoethyl) methacrytlate
Dimethylaminoethyl methacrylate
DMAEMA
Ethanol, 2-(dimethylamino)-, methacrylate
Methacrylic acid, 2-(dimethylamino) ethyl ester
2-Propenoic acid, 2-methyl, 2-(dimethylamino)ethyl ester

Purity: > 99.0 %

Physical and chemical properties:

Melting Point	-30 °C
Boiling Point	186 °C
Density	0.934 g/cm^3 (20 °C)
Vapour Pressure	1.10 hPa (25 °C)
Partition Coefficient (Log Pow)	1.13 (25 °C)
Water Solubility	106.1 g/L (25 °C)

2. GENERAL INFORMATION ON EXPOSURE

The production volume of MADAME was estimated as approximately 8,000 t/year in Japan and 48,000 t/year world-wide in 2000. Most of MADAME is industrially converted to the quaternary ammonium salt and polymerized for flocculant use in water treatment. Also, this chemical is used as a component monomer of copolymers in polymer industry, and the products are used for paper agents, coatings and others. Thus this chemical is not contained in consumer products in Japan. From uses and properties of this substance, estimated exposures are considered for the following 3 scenarios.

(1) Occupational exposure scenario
(2) Consumer exposure scenario
(3) Environmental exposure scenario

Migration of residual monomer from the polymer matrix is expected to be low. Nevertheless, the possibility of exposures cannot be excluded.

2.1 Environmental Fate

The Mackay level III fugacity model was employed to estimate the environmental distribution of MADAME in air, water, soil and sediment. This was considered the key study and the results are shown below.

Table 1. Estimated Distribution Under Three Emission Scenarios

	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	72.1 %	0.0 %	0.1 %
Water	13.6 %	99.7 %	5.7 %
Soil	14.2 %	0.0 %	94.2 %
Sediment	0.0 %	0.2 %	0.0 %

The results show that if MADAME is released into water, 99.7% stays in water, and it is unlikely to migrate into other compartments. When MADAME is released to air, 72.1% stays in air and, 13.6 % is transported to water and 14.2 % is transported to soil. However the calculation may include some uncertainty because of the weak dissociating property of the chemical.

Abiotically this chemical is stable to hydrolysis in water at pH 4 at 50 °C, whereas it is hydrolyzed at pH 7 and pH 9 at 25 °C with a half-life of 4.54 days and 3.31 hours, respectively [CERI Japan, 1997]. MADAME is hydrolysed to methacrylic acid (MAA) and 2-dimethylaminoethanol (DMAE).

MADAME is readily biodegradable (OECD 301E: BOD = 95.3% after 28days) [Roehm 1988a]. Both MAA and DMAE, produced by hydrolysis of MADAME, are also readily biodegradable. (MAA; BOD = 89 – 94% after 14days [CERI Japan, 1993], DMAE; BOD = 60.5 % after 14 days [CERI Japan, 1976])

MADAME is considered to have a low bioaccumulative potential based on its log Pow (1.13 at 25 °C) [CERI Japan, 1997].

If this chemical is released to air, indirect photodegradation is predicted to occur. The half-life is estimated to be 4 hours in the atmosphere.

2.2 Human Exposure

2.2.1 Occupational Exposure

Occupational exposures at production sites may occur by the inhalation route and dermal route.

The atmospheric concentration was measured at one production site [Japan Industrial Safety and Health Association (JISHA), 2000]. The monitored data are shown in Table 2.

Table 2: Workplace monitoring data for MADAME

Operation	Monitoring Data	Frequeny time/day	Working time hrs/time	Maximum EHE mg/kg/day
Drum Filling work	≤ 0.19 mg/m^3 (≤0.03 ppm)	1	0.50	1.70 x 10^{-3}
Maintenance work	≤ 0.19 mg/m^3 (≤0.03 ppm)	1	0.050	1.70 x 10^{-4}
Sampling	≤ 0.19 mg/m^3 (≤0.03 ppm)	1	0.025	8.48 x 10^{-5}

Total 1.95 x 10^{-3} mg/kg/day

EHE: Estimated Human Exposure

[Monitoring method]
Air sample was suctioned at the breathing zone of the worker at a suction rate of 0.4 L/min. for 5 min. and adsorbed through a collection can and analyzed by GC.

As shown in Table 2, the monitored exposure concentrations were below 0.19 mg/m^3 at the drum filling work, the maintenance work and the sampling. The highest daily intake (respiratory EHEinh) for a worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) assigned to the drum filling work without protection is calculated as 1.70 x 10^{-3} mg/kg/day. The duration of dermal exposure is assumed to be 0.50 hrs/day. EHEder for the worker who implement all daily operation through hands is calculated as 7.50 x 10^{-2} mg/kg/day, assuming that the work is classified as non-dispersive, direct handling, and contact level is incidental. Some production sites may have batchwise operations and release patterns may differ from the above description.

2.2.1.1 Occupational exposure limit of MADAME

There is no available official recommendation.

2.2.2 Consumer Exposure

MADAME is not considered to be contained in consumer products in Japan, because most of MADAME is industrially converted to the quaternary ammonium salt and polymerized to form flocculant to be used in water treatment. This chemical is also used as a component monomer of copolymers in polymer industry, and the products are used for paper agents, coatings and others. Migration of residual monomer from the polymer matrix is expected to be low. Nevertheless, the possibility of exposure cannot be excluded

2.2.3 Environmental Exposure

The production volume of MADAME was estimated as 8,000 t /year in Japan, and 48,000 t /year world-wide in 2000.

According to the monitoring data of Mitsubishi Gas Chemical Co., Inc., 38.5 kg/year of MADAME with 8.76×10^8 L of effluent is released yearly into seawater. Predicted local environmental concentration (PEC_{local}) is estimated as 4.39×10^{-5} mg/L, employing the following calculation model. In this case, the dilution factor of 1000 is adopted since most of MADAME released to the environment is discharged into sea.

$$\frac{\text{Amount of release } (3.85 \times 10^7 \text{ mg/y})}{\text{Volume of effluent after treatment } (8.76 \times 10^8 \text{ L/y}) \times \text{Dilution factor } (1000)}$$

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics and metabolism

The available data were limited. Two available studies were reviewed and described below.
Small quantities of methacrylates may readily be metabolized by saponification into the alcohol and methacrylic acid. The latter may form an acetyl-CoA derivative, which then enters the normal lipid metabolism [Clayton/Patty, 1993-1994]. The substance was rapidly hydrolysed to methacrylic acid (MAA) and N,N-dimethylaminoethanol (DMAE) when incubated with simulated saliva or simulated intestinal fluid *in vitro*. 90 % degradation was observed in simulated saliva after 4 hrs at 37 °C, 86 % degradation after incubation with simulated intestinal fluid for 4 hrs at 37 °C. Degradation was below 8% after incubation with simulated gastric fluid for 4 hours at 37 °C [Atochem, 1994]. However, no *in vivo* study is available.

3.1.2 Acute toxicity

There were various studies on the acute toxicity by different administration routes. Eleven reports on the acute toxicity via oral, dermal, inhalation or other routes to rats, mice or rabbits were reviewed and summarized in the table shown below. As for oral toxicity, the study by MHW [MHW Japan,1998] was considered to be the most reliable and identified as the key study because it was well conducted according to OECD TG 401 in compliance with GLP. The details of this study were as follows.

SD rats (5/sex/dose) were administered doses of 0 (vehicle), 500, 1000, 2000 mg/kg/day by gavage. Although raised patches and papillomatous hyperplasia in the forestomach were observed, no death occurred in the 2000 mg/kg/day dose. The oral acute toxicity LD_{50} is considered to be greater than 2000 mg/kg bw. As for dermal toxicity, the study on rats by Atochem [Atochem, 1992a] was conducted in accordance with OECD TG 402 in compliance with GLP and identified as the key study. At 2000 mg/kg dose, no mortality was observed although the symptom of hypokinesia, sedation dyspnea and skin irritation were observed. The dermal acute lethal dose is considered to be greater than 2000 mg/kg bw. Regarding toxicity by inhalation, although inhalation is a key route of exposure for this substance, only two values were reported [Izmerov, 1982] and these were not reliable because no detailed data were available. As to the acute toxicity by intraperioneal administration (i.p.), various values were reported in three tests on rats or mice. The severest value was 25 mg/kg bw for mice [NTIS, 1986].

Table 3. Acute toxicity of MADAME in experimental animals.

Route	Animals	Values	Type	References	Reliability
Oral	Rat	> 2,000 mg/kg bw	LD_{50}	MHW Japan, 1998	Reliable
Oral	Rat	= 1,751 mg/kg bw	LD_{50}	Izmerov, 1982	Not reliable
Oral	Rat	= 2,659 mg/kg bw	LD_{50}	Roehm, 1978	Reliable
Oral	Rat	= 1,550 mg/kg bw	LD_{50}	Kirk-Othmer, 1984	Not reliable
Dermal	Rat	> 2,000 mg/kg bw	LD_{50}	Atochem, 1992a	Reliable
Dermal	Rabbit	> 3,000 mg/kg bw	LD_{50}	Kirk-Othmer, 1984	Not reliable
Inhalation/ 4hrs	Rat	= 0.62 mg/L	LC_{50}	Izmerov, 1982	Not reliable
Inhalation/ 2hrs	Mouse	= 1.8 mg/L (280 ppm)	LC_{50}	Izmerov, 1982	Not reliable
i.p.	Rat	= 97 mg/kg bw	LD_{50}	Kirk-Othmer, 1984	Not reliable
i.p.	Rat	= 310 mg/kg bw	LD_{50}	Paulet, G., 1975	Not reliable
i.p.	Mouse	= 25 mg/kg bw	LD_{50}	NTIS, 1986	Not reliable

Human data

There is no available information.

Conclusions**:**

(Oral toxicity) At the highest dose of 2000 mg/kg, no mortality occurred. The acute oral LD_{50} of this chemical is considered greater than 2000 mg/kg bw. The acute toxicity of this substance can thereby be considered to be low.

(Dermal toxicity) Although hypokinesia, sedation, dyspnea and skin irritation were observed, no mortality occurred at 2000 mg/kg in rats. The acute dermal toxicity for rats is considered to be greater than 2000 mg/kg bw.

3.1.3 Repeat dose toxicity

Four studies of varied validity have been located. Two of them were oral administration studies and the other two were dermal and inhalation toxicity studies. One of the oral studies by MHW was identified as the key study because it was conducted according to OECD TG 422 in compliance with GLP [MHW Japan, 1998]. The other oral study was not reliable due to lack of data and was omitted from this assessment. The dermal study [Manabe, 1990] seems not reliable because no detailed data were available. The inhalation study [Gage, 1970] seems to be reliable and was identified as a key study.

(Oral Gavage) According to the OECD test guidelines for combined repeat dose and reproductive/developmental toxicity screening [OECD TG 422], SD (Crj: CD) rats was administrated with gavage doses of 0 (vehicle ; corn oil), 40, 200, and 1000 mg/kg/day. The dosing period for males was 43 days, and for females were 41 to 52 days, from 14 days before mating to the day 3 of lactation. The results are summarized below.

Table 4. The result of the repeated oral dose test

Dose mg/kg/day	Symptom
1000	Males : No death occurred. The following adverse effects were observed. *Late onset of twitching, chronic convulsion and the suppression of body weight gain. *By histopathological examination: Degeneration of nerve fibers in the brain and spinal cord, and hyperplasia of the mucosa, edema and inflammatory cell infiltration in the forestomach. Increase in the weight of the kidneys and livers without histopathological changes. *By blood examination: Slight increase in BUN and slight anemic changes such as decreases in erythrocyte counts, hemoglobin concentration and hematocrit value, associated with a significant increase in reticulocyte ratio. Females: 3 animals out of 12 died. The following adverse effects were observed in the surviving animals. * Late onset of twitching, chronic convulsion, suppression of body weight gain and decrease of food consumption during the lactation period. *By histopathological examination: Degeneration of nerve fibers in the brain and spinal cord, and hyperplasia of the mucosa in the gastric tract, edema and inflammatory cell infiltration in the forestomach and atrophy of the thymus. Increase in the weight of the kidneys and the adrenals without histopathological changes.
200	Males : No adverse effects were observed except for slight anemic changes such as decreases in hemoglobin concentration, hematocrit value and increase in reticulocyte ratio. Females: No effects were observed.
40	No effects for both sexes were observed.

Although slight anemic changes were observed in males of the 200 mg/kg/day group, the severity was considered toxicologically insignificant [MHW Japan, 1998]. The NOAEL for the repeat dose toxicity is considered to be 200 mg/kg/day for both sexes.

(Inhalation) Short-term vapor inhalation toxicity was studied in rats with a constant flow pump for 3 wks, 5 d/w, 6 h/d. At 250 ppm (1606 mg/m^3), nose and eye irritation, labored breathing were observed. The body weight gain was slow. There were no changes in the hematological parameters. No pathological (macroscopical and microscopical) effect on organs was observed. At 100 ppm (643 mg/m^3), no toxic effects were observed [Gage, 1970]. The NOAEL for repeated inhalation toxicity is considered to be 100 ppm (643 mg/m^3).

Human data

There is no available information.

Conclusions:

(Oral) At 1000 mg/kg/day, three of twelve females died. For both sexes, the adverse effects shown in the above table were observed. At 200 mg/kg/day, aalthough slight anemic changes such as decreases in hemoglobin concentration, hematocrit value and increase in reticulocyte ratio were observed in males, the severity was considered toxicologically insignificant. The NOAEL for repeat dose oral toxicity is considered to be 200 mg/kg/day for both sexes.

(Inhalation) At 100 ppm (643 mg/m^3), no toxic effects were observed. The NOAEL in the 3wks repeated dose inhalation toxicity study is considered to be 100 ppm (643 mg/m^3).

3.1.4 Genetic Toxicity

Genetic Toxicity
Seven reports were reviewed and summarized in the table shown below. These were two bacterial *in vitro* test reports, three non-bacterial *in vitro* test reports and two genetoxic *in vivo* test reports.

Table 5. Summary of genetoxicity studies

Type of test	Test system	Dose	Result	Reference
Bacterial *in vitro* test				
Reverse mutation TG 471 & 472	*S. typhimurium* (strains TA100, TA1535, TA98, TA1537) *E. coli* WP2 uvr A	Up to 5000 ug/plate	With MA *: Negative for all strains at all doses.	MHW Japan, 1998
		Up to 5000 ug/plate Toxicity was observed at 3500 ug/plate and more.	Without MA: Positive only at 2500 and 3000 ug/plate for TA1537. Negative for all other strains at all doses.	
	S. typhimurium (strains TA1535, TA1537, TA1538, TA98 and TA100)	Up to 5000 ug/plate	Negative (+ & - MA)	Atochem, 1991a
Non Bacterial *in vitro* test				
Chromosomal aberration test TG 473	CHL/IU cells Human lympocytes	Up to 1.6 mg/mL Up to 1.57 mg/mL	Positive (+ & - MA) Positive (+ & - MA)	MHW Japan, 1998 Atochem, 1991b
HPRT assay TG 476	V79 Chinese hamster cells	Up to 2.0 mg/mL with S9 Mix.	Negative (+ & - MA)	Atochem, 1992b
Genetic *in vivo* test				
Micronucleus Test TG 474	Mice (i. p)	200 mg/kg bw Two administrations, 24 hrs interval.	Negative	Atochem, 1993
	Mice (p. o)	Up to 1000 mg/kg bw	Negative	Rohem, 1989

* MA: Metabolic activation

Bacterial tests

Two studies were reviewed. These two studies were conducted according to OECD TG 471 & TG 472 in compliance with GLP and were identified as the key studies [MHW Japan, 1998] [Atochem, 1991a].

1) MHW, Japan (1998): Screening Mutagenicity Testing of Chemicals
The test was conducted two times for all cells with and without S9 and the results were positive without S9 at 2500 ug/plate and higher for TA 1537 and TA 98. Then the confirmation test was conducted for *S. typhimurium* TA 1537 and TA 98 without S9. Toxic effects were observed at 3500 ug/plate and higher concentrations to TA 98 and TA 1537 without S9 mix.

The result of the confirmation test was positive only for TA 1537 at 2500 and 3000 ug/plate. The number of the induced revertant colonies per mg was calculated as 3.6.

2) Atochem (1991a):
Atochem reported that MADAME was negative in any of *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 at doses of 10, 100, 1000, 2500, and 5000 ug/plate with and without S9.

Non-bacterial in vitro tests

Three studies were reviewed. Two studies were chromosomal aberration tests by OECD TG 473 on cultured Chinese hamster lung cells [MHW Japan, 1998] and on human lymphocytes [Atochem, 1991b].
Another study was conducted according to OECD TG 476: HPRT/V 79 [Atochem, 1992b]. These three tests were conducted in compliance with GLP and were identified as key studies. The three studies are summarized below.

1) MHW, Japan (1998): Chromosomal aberrations assay on cultured Chinese hamster lung cells
After 24 hrs and 48 hrs continuous treatment without S9, structural chromosomal aberrations (including gap) were induced at 625 ug/mL with 88.5% and 76.5% respectively. The number of cells with aberrations excluding gaps were 86.5% and 74.0% respectively. Cytotoxicity was observed at 625 ug/mL and 313 ug/mL. By the 6 hrs short-term treatment without S9, concentration-dependent structural chromosomal aberrations (including gap) were induced at 200 ug/mL, 400 ug/mL and 600 ug/mL with 6.5 %, 49.5 % and 87.5 % respectively. The number of cells with aberrations excluding gaps were 6.5%, 46.0% and 86.0% respectively. By the 6 hrs short-term treatment with S9, concentration-dependent structural chromosomal aberrations (including gaps) were induced at 800 ug/mL, 1400 ug/mL and 1600 ug/mL with 13.5 %, 99.5 % and 100 % respectively.
The number of cells with aberrations excluding gaps were 13.0%, 99.5% and 100.0% respectively.
Polyploidy was not induced under any of these conditions. At more than 800 ug/mL of the 6 hrs short-term treatment without S9 mix and at more than 1600 ug/mL with S9 mix, cytotoxicity was observed. As a result, MADAME is considered to induce chromosomal aberrations with and without metabolic activation. However, the aberrations were mainly chromatid breaks and chromatid exchanges.

2) Atochem (1992b): Chromosomal aberrations assay on human lymphocytes
The dose levels were up to 1572 ug/mL (maximum solubility). The cells sampled at 20 hours after the start of the treatment were analysed for chromosomal aberrations. At the higher two concentrations, namely 1179 ug/mL without S9 and 1572 ug/mL with S9, this chemical induced aberrations which were significantly different from those observed in the concurrent solvent controls. No exchange-type aberrations were observed, but only deletion-type aberrations were seen. The number of cells with aberrations excluding gaps (average of two tests) at 1179 ug/mL without S9 and 1572 ug/mL with S9 were 11.0% and 7.5% respectively. No marked mitomic inhibition was evident in any of the doses analysed in this study. The mitomic index at 1179 ug/mL without S9 and 1572 ug/mL with S9 was 2.3 % and 6.2 % respectively. It is concluded that MADAME may induce chromosomal aberrations in the human peripheral blood lymphocytes with and without metabolic activation.

3) Atochem (1992b): HPRT/V79 Chinese hamster cell test
The test was conducted at concentrations from 31.25 to 2000 ug/mL. With and without metabolic activation, MADAME showed some cytotoxic effects at concentrations higher than 250 ug/mL, but no increase in the mutation frequencies were observed at any concentrations tested. Under these experimental conditions, MADAME was not genotoxic.

Genetoxic in vivo tests

Two micronucleus assays were reviewed. These two studies were conducted according to OECD TG 474 in compliance with GLP and were identified as key studies [Atochem, 1993], [Roehm, 1989]. The summary of the studies is shown below.

1) Atochem (1993): on the clastogenic potential of MADAME in OF1 mice
The animals (5 males and 5 females per group) received two administrations separated by 24 hrs, of 200 mg/kg by the intraperitoneal route. Cyclophosphamide at the dose level of 25 mg/kg (two times i.p. injection) served as the positive control. The test animals were killed at 24 or 48 hrs after the 2nd administration and the bone marrow smears were examined for the presence of micronuclei in 2000 polychromatic erythrocytes per mouse and for the PCE/NCE ratio. The number of the micronucleated polychromatic cells in the dosed animals was not significantly different from that of the animals in the control groups.
MADAME did not induce cytogenetic damage to the bone marrow cells of mice in this test.

The summary of the test results is shown below.

Time of sacrifice: 24 hrs after the 2nd administration

Group	doses	MPE/PE	PE/NE ratio
---	(mg/kg)	Mean (SD)	Mean (SD)
vehicle	-----	2.0 (0.8)	0.7 (0.2)
Test substance	200	1.9 (1.1)	0.6 (0.2)
CPA	25	18.2 (3.8)#	0.4# (0.1)

Time of sacrifice: 48 hrs after the 2nd administration

Group	doses	MPE/PE	PE/NE ratio
	(mg/kg)	Mean (SD)	Mean (SD)
vehicle		1.9 (0.8)	0.9 (0.4)
Test substance	200	1.7 (1.0)	1.2 (0.6)

10 animals(5 males, 5 females) per group
: $P < 0.001$
Vehicle: physiological solution
CPA : cyclophosphamide
PE : polychromatic erythrocytes
NE : normochromatic erythrocytes
MPE/PE: micronucleated polychromatic erythrocytes/1000 Polychromatic erythrocytes.
(SD) : standard deviation.

2) Roehm (1989): on the clastogenic potential of MADAME in NMRI mice
The maximum tolerated dose of 1000 mg/kg bw, dissolved in water, was administered by oral gavage to 3 groups of 10 NMRI mice (5 males and 5 females). As negative control, distilled water was served. As positive control, cyclophosphamide in physiological serum (NaCl) was dosed at 40 mg/kg. The test mice were killed at 24, 48 or 72 hrs after the administration. The bone marrow smears were examined for the presence of micronuclei in 1000 polychromatic erythrocytes per mouse and for the PCE/NCE ratio. No significant increase of micronuclei was observed compared to the negative control group. No micronuclei induction due to MADAME was observed.

The summary of the test results is shown below.
Sampling time: 24 hrs

Group	Dose mg/kg bw	PCEs with Micronuclei (%)	Micronuclei in 1000 PCE (Range)	PCE/NCE (mean)
Solvent	0	0.06	0 – 2	1000 / 554
Test article	1000	0.03	0 – 2	1000 / 653
CPA	40	0.75	1 – 13	1000 / 742

Sampling time: 48 hrs

Group	Dose mg/kg bw	PCEs with Micronuclei (%)	Micronuclei in 1000 PCE (Range)	PCE/NCE (mean)
Solvent	0	0.04	0 – 2	1000 / 680
Test article	1000	0.04	0 – 1	1000 / 744

Solvent: distilled water
CPA : cyclophosphamide
PCE : polychromatic erythrocytes
NCE : normochromatic erythrocytes

Conclusions:

Two independent gene mutation tests in bacteria resulted in negative results except for one positive result in *S. typhimurium* TA1537 at 2500 ug/plate without metabolic activation in one study. A HPRT study with Chinese hamster cultured cells was negative. Chromosomal aberration tests *in vitro* and a human lymphocyte test were positive for clastogenicity with and without metabolic activation. Two *in vivo* micronucleus assays by i.p. or gavage respectively, however, are negative for clastogenicity. Based on the weight of evidence, it is concluded that this chemical is not genotoxic *in vivo*.

3.1.5 Carcinogenicity

No data are available.

3.1.6 Reproduction/developmental toxicity

There was only one study available. The combined repeat dose and reproductive toxicity study by the oral route [MHW Japan, 1998] was identified as the key study because it was conducted according to OECD TG 422 in compliance with GLP.

Reproductive and developmental study: SD (Crj: CD) rats received gavage doses of 0 (vehicle; Corn oil), 40, 200 and 1,000 mg/kg/day, for males for 14 days before mating and for females from 14 days before mating to day 3 of lactation. The animals were sacrificed on day 4 of lactation for females. There were no effects on the reproductive parameters such as the mating index, the fertility index, the number of corpora lutea or implantations, the implantation index, the delivery index, the gestation index and the gestation length or the parturition. Three females in the 1000 mg/kg/day group, however, lost all of their pups during the lactation period. Also it should be noted that females in the 1000 mg/kg/day group showed many adverse effects in the repeated oral dose test such as death of 3 animals out of 12, late onset of twitching, chronic convulsion, the

suppression of body weight gain, degeneration of nerve fibers in the brain and spinal cord, hyperplasia of the mucosa in the gastric tract, the edema and inflammatory cell infiltration in the forestomach, atrophy of the thymus, increase in the weight of the kidneys and the adrenals without histopathological changes. The pups from the females in the 1000 mg/kg showed lower body weights and were lower in the viability index due to maternal nursery activity. It is reported that by external inspection, no abnormalities were found. However, a lower body weight gain and a lower viability index were observed in the pups from the females of the 1000 mg/kg/day group. The NOAEL for the reproductive/developmental toxicity is considered to be 200 mg/kg/day.

Human Data

There is no available information on humans.

Conclusions:

The NOAEL of this chemical for the reproductive/developmental toxicity is considered to be 200 mg/kg/day.

3.1.7 Other human health related information

1) Irritation (skin and eye) and sensitizing potential

The summaries of these studies are shown in the table below.

Table 6:The summary of other human health related information

Species	Method	Result	Reference
Irritation(skin)			
Rabbit	Occlusive patch Federal Register (USA)-29 FR13009, 1964	Corrosive. Primary irritation score: 8.0	Atochem, 1980
Rabbit	Draize test	Highly irritating Draise index: 5.9 of 8 (reevaluated according to OECD 404)	Roehm, 1977
Guinea pig	No data	Irritation occurs even when using silicon or 5% Zn cream.	Roehm, 1977
Irritation (eye)			
Rabbit	Federal Register (USA)-9 FR13009, 1964	Corrosive:	Atochem, 1980
Sensitization			
Guinea pig	OECD TG 406 Split adjuvant	Negative: No cutaneous reactions	Atochem, 1991c

(Skin irritation) There are three reports available. Among them, the study by Atochem was identified as the key study because it was conducted according to the recommendations of the Federal Hazardous Substances Labelling Act Regulations, Section 191.11, published in the Federal Register (USA)-29 FR13009, 1964 [Atochem, 1980]. MADAME was administrated to the intact

and abraded skin of New-Zealand albino rabbits at the dose level of 0.5 mL per animal under the occlusive patch for 24 hours.
The cutaneous reactions were observed just after the removal of the patch and after 72 hours. Severe erythema, oedema and necrosis were observed after the test and these symptoms persisted to the inspection after 72 hours of the test. A primary irritation score of 8.0 was obtained. Under these test conditions, MADAME was considered to be corrosive to the skin.

(Eye irritation) The only study available was considered to be reliable because it was conducted in accordance with the recommendations of the Federal Hazardous Substances Labelling Act [Atochem, 1980]. Severe cornea, iris and conjunctive lesions were displayed in all animals within 2 hours after the instillation of 0.1mL MADAME. MADAME was considered to be corrosive to eyes.

(Sensitization) There was only one study available. The sensitizing potential of MADAME was evaluated by a modified Magnusson and Kligman method according to the OECD guideline No. 406 with the principles of Good Laboratory Practice and was identified as a key study [Atochem, 1991c].

The general behaviour and the body weight gain of the animals were not influenced by the treatment. After the challenge test, a very slight erythema (score 1) was observed on the right flank of 16 out of 20 treated animals. As the cutaneous reactions were very slight and the reactions observed at the 24 hours scoring period were reversible at the 48 hours scoring period, the cutaneous reactions were attributed to orthoergique reaction. No cutaneous reaction likely to be caused by a sensitization potential of MADAME were observed.

2) Other toxic information

Other available toxic information are summarized in the table shown below.

Table 7. The summary of other toxic information

Species	Method	Result (Symptoms)	Reference
Pharmacology			
Dogs (anesthetized)	Intravenous administration 0.0026 to 0.028 mL	Elicited a hypertensive effect. Produced a 28-67 % increase in blood pressure with small doses.	Mir, 1974
Rabbit (isolated and perfused)	10^{-3}, 10^{-4}, 10^{-5} (v/v) concentration. Examined the activity.	Reduction of the heart rate, the force of contraction and the coronary flow rate. Cardiac standstill at a concentration of 10^{-4} (v/v).	Mir, 1973
Guinea pig (isolated)	4 x10^{-5}, 2 x 10^{-5} and 10^{-5} v/v concentration. Examined the ileum activity.	The ileum was stimulated by this chemical, the effect was not antaginised by atropine.	Mir, 1973
Others			
Cytotoxicity	Cell growth inhibition in Balb/c 3T3 Fibroblasts	ID50 > 100 umol/L (endpoints observed: inhibition of DNA synthesis, protein synthesis, total ptotein content, irreversible inhibition of cell metabolism)	Hanks, 1975
Enzyme inhibition *in vitro*	Choline esterase inhibition	The substance did not inhibit cholinesterase activity of the isolated enzyme or in rat brain preparations *in vitro*.	Rowell, 1976

In general, the mode of pharmacological action is cholinergic. However, the mode of action in rat brain and nervous cells found in the repeated dose study has not been elucidated.

3) Information on structurally related chemicals:

Methyl methacrylate (MMA) (CAS Nr. 80-62-6)

MADAME belongs to esters of methacrylic acid. However, MADAME is unique in the hydrophilic and alkaline nature and relatively low volatility (vapour pressure), that makes a substantial difference from other analogues in the toxicological properties. The most representative chemical among the analogues is MMA. According to the SIDS of MMA, inhaled MMA is metabolised by local tissue esterase. Inhalation is the most relevant route to evaluate the toxicity and the main effect is a degeneration of the olfactory region of the nose in rat or mouse studies. Other systemic toxicity effects are degenerative and necrotic lesions in liver, kidney, brain and atrophic changes in spleen and bone marrow, part of which may have been modulated by physiological changes in experimental animals. These effects were not seen in chronic studies up to 1000 ppm. Oral administration to rats resulted in a NOAEL of 200 mg/kg/day.

MMA has *in vitro* the potential of mutagenic effects, especially clastogenicity. However, this potential is limited to high doses with strong toxic effects. Furthermore, the negative *in vivo* micronucleus test and negative dominant lethal assay indicate that this potential is not expressed *in vivo*. There is no relevant concern regarding carcinogenicity of MMA in humans and animals. Epidemiology data on increased tumour rates in exposed cohorts are of limited reliability and cannot be related to MMA as the solely causal agent. MMA did not reveal an effect on male fertility when animals had been exposed to up to 9000 ppm.

From the available developmental toxicity investigations, including an inhalation study according to OECD guideline 414, no teratogenicity, embryotoxicity or fetotoxicity has been observed at exposure levels up to and including 2028 ppm (8425 mg/m^3).

Human data

No data are available.

3.2 Initial Assessment for Human Health

Human Health Hazards

This chemical is supposedly metabolized to methacrylic acid (MAA) and N,N-dimethylaminoethanol (DMAE). Then the MAA may form an acetyl-CoA derivative, which then enters the normal lipid metabolism. The oral LD_{50} in rats is greater than 2000 mg/kg. This chemical is considered to be severely irritating or corrosive to skin and eye. This chemical does not have a sensitizing potential.

The OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422] was conducted in rats at doses of 0, 40, 200 and 1000 mg/kg/day administered by gavage. For both sexes, a clear systemic toxicity was demonstrated only at 1000 mg/kg/day. Late onset of twitching, chronic convulsion and the suppression of body weight gain were observed. Three females out of 12 died. Histopathological examination revealed degeneration of nerve fibers in the brain and spinal cord, and hyperplasia of the mucosa, edema and inflammatory cell infiltration in the forestomach in both sexes. Increases in organ weights without histopathological changes were observed in the kidneys of both sexes, the livers of males, and the adrenals of females in this group. For the males in this group, BUN was slightly increased and anemic changes such as decreases in erythrocyte counts, hemoglobin concentration and hematocrit value, associated with a significant increase in reticulocyte ratio were observed. In males from the 200 mg/kg/day group, only slight anemic changes such as those observed at 1000 mg/kg/day were seen, but the severity was considered toxicologically insignificant. The NOAEL for the repeat dose toxicity is considered to be 200 mg/kg/day.

A repeated inhalation study for 3 weeks revealed a NOEL of 100 ppm. Nose and eye irritation was observed at 250 ppm (LOEL).

Two independent gene mutation tests in bacteria [OECD TG 471 & 472] resulted in negative results except for a positive result in *S. typhimurium* TA 1537 at 2500 ug without metabolic activation system in one study. A HPRT study on Chinese hamster cultured cell [OECD TG 476] was negative. A chromosomal aberration test *in vitro* [TG 473] and a human lymphocyte test were positive with and without metabolic activation. However two *in vivo* studies [micronucleus assay, OECD TG 474] by i.p. or gavage respectively, gave negative results. Based on the weight of evidence, it is concluded that this chemical is not genotoxic *in vivo*.
In the above-described OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], there was no sign of reproductive toxicity up to 1000 mg/kg/day for males. Three females in 1,000 mg/kg/day, however, lost all of their pups in lactation period. As to the developmental effect, the pups born from the females in 1000 mg/kg/day group showed a lower body weight although no external abnormalities were observed. The NOAEL of the reproductive/developmental toxicity is considered to be 200 mg/kg/day for both parents and offspring.

4. EFFECTS ON THE ENVIRONMENT

4.1 Aquatic Effects

MADAME has been tested in a limited number of aquatic species. Results are summarised in Table 8. All the data shown here were derived from experiments conducted under GLP, and the chemical concentrations in the testing media were analyzed during the course of the experiments. The lowest chronic result was 4.35 mg/L (*Daphnia magna* 21d-NOEC, reproduction).

Table 8: Summary of effects of MADAME on aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
algae			
Green alga (*Selenastrum capricornutum*)	72 h (op)	EC_{50} (bms) = 41.6 (nc) NOEC (bms) = 18 (nc)	MOE, Japan 1997
Invertebrates			
Water flea (*Daphnia magna*)	48 h (op,ss)	EC_{50} (imm) = 33 (mc)	MOE, Japan 1997
	----------	----------	----------
	21 d (op,ss)	LC_{50} = 16.6 (mc) EC_{50} (rep) = 7.86 (mc) NOEC (rep) = 4.35 (mc)	MOE, Japan 1997
Fish			
Medaka (*Oryzias latipes*)	96 h (op,ss) 14 d (ss)	LC_{50} = 19.1 (mc) LC_{50} = 5.26 (mc)	MOE, Japan 1997

op: open system
f: flow through ss: semi-static
nc: nominal concentration
mc: calculated based on measured concentrations, because some data of measured concentrations were < 80 % of nominal concentrations.
bms: biomass imm: immobilization rep: reproduction

The results of the algal inhibition test with *Selenastrum capricornutum* are based on nominal concentrations of MADAME. Analytical measurements showed that concentrations of MADAME decreased during the test from 80.9-88.2% of nominal concentrations at the start of the test to 0.39-2.18 % of nominal concentrations at the end of the test. The pH in the test system was 9.03-9.25 at the start of the test and 7.9-9.13 at the end of the test. As the test substance hydrolyses rapidly (half-life 4.54 days at pH 7 and 3.31 hours at pH 9), it can be assumed that the observed effects are partially due to the hydrolysis products methacrylic acid and N,N-dimethylaminoethanol.

4.2 Toxicity to Terrestrial Organisms

One study was found for terrestrial toxicity in birds on MADAME. The value of LD50 (18hr) was described as 98 mg/kg for *Agelais phoenicus* [Schafer 1983].

4.3 Other

A toxicity test in bacteria was reported on MADAME. The value of EC10 (18hr) in *Pseudomonas putida* was 42.7 mg/L [Roehm (1988b)].

4.4 Initial Assessment for the Environment

The results of a generic fugacity model (Mackay level III) show that if MADAME is released into water, 99.7 % stays in water and 0.2 % is transported to sediment. When MADAME is released to air, 72.1 % stays in air, 13.6 % is transported to water, and 14.2 % is transported to soil. This chemical is readily biodegraded [Roehm, 1988] and is considered to have a low bioaccumulative potential based on its log Pow (1.13 at 25 °C) [CERI, Japan: 1997].

Information on the aquatic toxicity of MADAME is limited. Results for algae, fish and/or aquatic invertebrates are summarized below.
The toxicity results (growth inhibition: [OECD TG 201]) for algae (*Selenastrum capricornutum*) were 41.6 mg/L (72 h-EC_{50}) and 18 mg/L (72 h-NOEC). The acute (immobility: [OECD TG 202]) and chronic (reproduction: [OECD TG 211]) toxicity results for daphnids are 33 mg/L (48h-EC_{50}), 16.6 mg/L (21d-LC_{50}), 7.86 mg/L (21d-EC_{50}), and 4.35 mg/L (21d-NOEC), respectively. The acute LC_{50} (96 hr: [OECD TG 203]) and prolonged LC_{50} (14 d: [OECD TG 204]) for fish (Medaka; *Oryzias latipes*) were 19.1 mg/L and 5.26 mg/L, respectively.
Due to the half-life of 2-Dimethylaminoethyl methacrylate in water at the test conditions the aquatic toxicity of the hydrolysis products have to be considered.

Toxicity data for aquatic organisms:

Methylacrylic acid CAS No.: 79-41-4 (EU Risk Assessment Report)

- Fish (*Oncorhynchus mykiss*): 96 h LC50 = 85 mg/l
- *Daphnia magna*: 48 h EC50 >130 mg/l
  21 d NOEC 53 mg/l (parent mortality, reproduction rate)
- Algae (*Selenastrum capricornutum*): 72 h E_bC50 = 20 mg/l
  72 h NOEC = 8.2 mg/l

2-Dimethylaminoethanol CAS No.: 108-01-0 (SIAR)

- Fish (Fathead minnow): 96 h LC50 = 81 mg/l
- *Daphnia magna*: 48 h EC50 = 98.77 mg/l
- Algae (Scenedesmus): 72 h EC50 = 35 mg/l

All toxicity data from both the mother substance and the hydrolysis products are in the same order of magnitude.

5. Conclusions and Recommendations

5.1 Conclusions

Exposure

The production volume of MADAME was reported as approximately 8,000 t/year in Japan and 48,000 t/year world-wide in 2000. MADAME is produced in a fully-closed system. Most of MADAME is industrially converted to the quaternary ammonium salt and polymerized for flocculant use in the water treatment. Also, this chemical is used as a component monomer of copolymers in polymer industry, and the products are used for paper agents, coatings and others. The workplace exposures during those application processes are controlled.
Fugacity modeling (Mackay level III) predicts that MADAME released to water unlikely will migrate into other compartments. MADAME is readily biodegradable and not persistent in the water phase. When this chemical is released to air, 72 % stays in air and 28 % is transported into water and soil.
From production, uses and properties of this substance, estimated exposures are considered in 3 scenarios;
(1) Occupational exposure scenario: inhalation of vapor without breathing protection in the factory;
Vapor level was 0.19 mg/m^3 as measured at the drum filling workplace;
EHEinh = 0.0017 mg/kg/day and EHEder = 0.075 mg/kg/day, using estimation methods.
(2) Consumer exposure scenario: Exposure is controlled because of the non dispersive use.
Migration of residual monomer from the polymer matrix is expected to be low. Nevertheless, the possibility of exposures cannot be excluded.
(3) Environmental exposure scenario: emission to aquatic compartment from waste water;
PEClocal water = 0.0000439 mg/L using estimation methods.

Hazards to the Environment

MADAME is readily biodegradable (OECD 301E; BOD: 95.3 % after 28 days), and has a low bioaccumulation potential based on its log Pow (1.13). Abiotically this chemical is stable at pH 4, whereas it is hydrolyzed at pH 7 and at pH 9 with half-lifes of 4.54 days and 3.31 hours, respectively.

This chemical has been tested in a limited number of aquatic species including algae, daphnid and fish. The toxicity results (growth inhibition: [OECD TG 201]) for algae (*Selenastrum capricornutum*) were 41.6 mg/L (72 h-EC_{50}) and 18 mg/L (72 h-NOEC). The acute (immobility: [OECD TG 202]) and chronic (reproduction: [OECD TG 211]) toxicity results for daphnids are 33 mg/L (48h-EC_{50}), 16.6 mg/L (21d-LC_{50}), 7.86 mg/L (21d-EC_{50}), and 4.35 mg/L (21d-NOEC), respectively. The acute LC_{50} (96 hr: [OECD TG 203]) and prolonged LC_{50} (14 d: [OECD TG 204]) for fish (Medaka; *Oryzias latipes*) were 19.1 mg/L and 5.26 mg/L, respectively.

Human health

The acute toxicity of this chemical is low because LD_{50} values are greater than 2000 mg/kg by the oral route.
This chemical is severely irritating or corrosive to skin and eye. Although only one study was available, this chemical had no sensitizing effect [OECD TG 406].

The NOAEL for the repeat dose toxicity by the combined repeat dose and reproduction / developmental toxicity screening test [OECD TG 422], is considered to be 200 mg/kg/day for both

sexes. A repeated inhalation study for 3 weeks revealed a NOEL of l00 ppm. Nose and eye irritation was observed at 250 ppm (LOEL).

In the above-described OECD combined repeat dose and reproduction / developmental toxicity screening test [MHW Japan, 1998/OECD TG 422], there was no sign of reproductive or developmental toxicity up to 1000 mg/kg/day for males. Three females in the 1000 mg/kg/day group, however, lost all of their pups in the lactation period. As to the developmental effect, the pups born from the females in the 1000 mg/kg/day group showed a lower body weight gain although no external abnormalities were observed. The NOAEL for reproductive/developmental toxicity is considered to be 200 mg/kg/day for both parents and offspring.

Two independent gene mutation tests in bacteria [OECD TG 471 & 472] resulted in negative results except for a positive result in *S. typhimurium* TA 1537 at 2500 ug without metabolic activation system in one study.
A HPRT study on Chinese hamster cultured cell [OECD TG 476] was negative. A chromosomal aberration test *in vitro* [MHW Japan, 1998/TG 473] and a human lymphocyte test were positive with and without metabolic activation. However two *in vivo* studies [micronucleus assay, OECD TG 474] by i.p. or gavage respectively, negative gave negative results. Based on the weight of evidence, it is concluded that this chemical is not genotoxic *in vivo*.

5.2 Recommendations

The chemical is currently of low priority for further work.

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SIDS Dossier

Existing Chemical	:	ID: 2867-47-2
CAS No.	:	2867-47-2
EINECS Name	:	2-dimethylaminoethyl methacrylate
EINECS No.	:	220-688-8
TSCA Name	:	2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester
Molecular Formula	:	C8H15NO2

Producer Related Part

Company	:	MITSUBISHI . GAS CHEMICAL CO., INC.
Creation date	:	11.10.2001

Substance Related Part

Company	:	MITSUBISHI . GAS CHEMICAL CO., INC.
Creation date	:	11.10.2001
Memo	:	MADAME SIAM 14
Printing date	:	10.01.2002
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Date of last Update	:	10.01.2002
Number of Pages	:	64
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD and Company Information

Type	:	lead organisation
Name	:	Mitsubushi Gas Chemical Company, Inc.
Partner	:	
Date	:	
Street	:	Mitsubishi Bldg. 5-2, Marunouchi 2-chom e, Chiyoda-ku
Town	:	100-8324 Tokyo
Country	:	Japan
Phone	:	+81-3-3283-4821
Telefax	:	+81-6-6201-2857
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
09.01.2002		

Type	:	cooperating company
Name	:	Atofina
Partner	:	
Date	:	
Street	:	4-8, cours Michelet, La Defence 10
Town	:	F-92091 Paris La Defence Cedex
Country	:	France
Phone	:	+33 1 49 00 71 97
Telefax	:	+33 1 49 00 50 58
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

Type	:	cooperating company
Name	:	Degussa, Roehm GmbH & Co.
Partner	:	
Date	:	
Street	:	KG, Kischenallee,
Town	:	D-64293 Darmstadt
Country	:	Germany
Phone	:	+49 6151 184241
Telefax	:	+49 6151 183213
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

Type	:	cooperating company
Name	:	Mitsubishi Rayon Co., Ltd.
Partner	:	
Date	:	
Street	:	1-6-41 Konan, Minato-ku,
Town	:	108-8506 Tokyo
Country	:	Japan
Phone	:	+81 3 5495 3009
Telefax	:	+81 3 5495 3246
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

Type	:	cooperating company

Name	:	Mitsui Chemicals, Inc.
Partner	:	
Date	:	
Street	:	Kasumigaseki, Chiyoda-ku,
Town	:	100-6070, Tokyo
Country	:	Japan
Phone	:	+81 3 3592 4340
Telefax	:	+81 3 3592 4236
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

Type	:	cooperating company
Name	:	Sanyo Chemical Industries, Ltd.
Partner	:	
Date	:	
Street	:	11-1 Ikkyo, Nomoto-cho, Higashiyama-ku
Town	:	605-0995 Kyoto
Country	:	Japan
Phone	:	+81 75 541 6362
Telefax	:	+81 75 531 2139
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

Type	:	cooperating company
Name	:	Ciba Specialty Chemicals Inc.
Partner	:	
Date	:	
Street	:	Klybeckstrasse 141
Town	:	CH-4002 Basel
Country	:	Switzerland
Phone	:	+41 61 636 55 29
Telefax	:	+41 61 636 78 78
Telex	:	
Cedex	:	
Source	:	Mitsubushi Gas Chemical Company, Inc.
08.01.2002		

1.0.2 Location of Production Site

1.0.3 Identity of Recipients

1.1 General Substance Information

Substance type	:	organic
Physical status	:	liquid
Purity	:	% w/w
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000		

1.1.0 Details on template

1.1.1 Spectra

1.2 Synonyms

MADAME
Source : Mitsubushi Gas Chemical Company, Inc.
09.10.2001

2-(Dimethylamino)ethanolmethacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

2-(N,N-Dimethylamino)ethylmethacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

2-Dimethylaminoethyl methacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

2-Dimethylaminoethyl-2-methyl-propenoate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

2-Dimethylaminoethyl-2-methylpropenoate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

2-Propenoic acid, 2-methyl, dimethylaminoethyl ester
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

beta-(N,N-Dimethylaminoethyl) methacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

beta-Dimethylaminoethyl methacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

DAM
Source : Mitsubushi Gas Chemical Company, Inc.
09.10.2001

Dimethylaminoethyl methacrylate
Source : SNF S.A. Saint-Etienne
Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
04.06.1998

DMAEMA
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

31.05.1994

Ethanol, 2-(dimethylamino), methacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

MADAME ; 2-(Dimethylamino)ethanolmethacrylat; 2-(N,N-Dimethylamino)ethylmethacrylat; 2-Dimethylaminoethyl-2-methyl-2-propenoat; 2-Dimethylamino-2-methylpropenoat; Dimethylaminoethylmethacrylat; Ethanol, 2-(dimethylamino)-, methacrylat
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
08.06.1994

Methacrylic acid dimethylaminoethylester
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

Methacrylic acid, 2-(dimethylamino)ethyl ester
Source : SNF S.A. Saint-Etienne
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
04.06.1998

Methacrylsaueredimethylaminoethylester; N,N-Dimethylaminoethylmethacrylat; beta-(N,N-Dimethylamino)ethylmethacrylat; beta-Dimethylaminoethylmethacrylat
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
22.12.1993

N,N-Dimethylaminoethyl methacrylate
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.05.1994

1.3 Impurities

CAS-No : 108-01-0
EINECS-No : 203-542-8
EINECS-Name : 2-dimethylaminoethanol
Contents : < .5 % w/w
Remark : raw material
Source : Mitsubushi Gas Chemical Company, Inc.
12.12.2001

CAS-No : 80-62-6
EINECS-No : 201-297-1
EINECS-Name : methyl methacrylate
Contents : < .5 % w/w
Remark : raw material
Source : Mitsubushi Gas Chemical Company, Inc.
12.12.2001

1.4 Additives

CAS-No : 150-76-5

EINECS-No : 205-769-8
EINECS-Name : mequinol
Contents : .03 - .3 % w/w
Remark : stabilising agent
07.12.2001

1.5 Quantity

Remark : 8,000 t/year in Japan and 48,000 t/year world-wide in 2000
Source : Mitsubushi Gas Chemical Company, Inc.
08.01.2002

Production during the last 12 months :
Import during the last 12 months :
Quantity : 10 000 - 50 000 tonnes in
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.6.1 Labelling

Labelling : as in Directive 67/548/EEC
Symbols : Xn
Nota : D
Specific limits : yes
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
(36/38) Irritating to eyes and skin
(43) May cause sensitization by skin contact
S-Phrases : (2) Keep out of reach of children
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of water...
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
08.01.2002

1.6.2 Classification

Classification : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Classification : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (36/38) Irritating to eyes and skin
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

Classification : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (43) May cause sensitization by skin contact
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
11.02.2000

1.7 Use Pattern

Type : type
Category : Non dispersive use
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
11.02.2000

Type : type
Category : Use in closed system
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
11.02.2000
Type : industrial
Category : Chemical industry: used in synthesis
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
11.02.2000
Type : industrial
Category : Polymers industry
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
11.02.2000
Type : use
Category : Intermediates
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
11.02.2000

1.7.1 Technology Production/Use

1.8 Occupational Exposure Limit Values

Type of limit : Short Term Occupational Exposure Limit (OEL STEL)
Limit value : 1 ppm (6.43 mg/m3)
Remark : Proposed by ATOFINA's Occupational Limit Setting Committee)
Source : ATOFINA Paris La Defense France d'ELF
24.06.1998
Remark : No data available on Occupational Exposure Limit Values
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
08.06.1994

1.9 Source of Exposure

Remark : Occupational exposures at production sites may occur by the inhalation route and dermal route.

The atmospheric concentration was measured at one production site [Japan industrial Safety and Health Association (JISHA), 2000]. The monitored data are shown below.

Operation	Monitoring Data	Frequency Time/day	Working time hrs/time	Max. EHE mg/kg/day
Drum Filling	≤ 0.19 mg/m3 (≤ 0.03 ppm)	1	0.50	1.70 x 10-3
Drum Filling	≤ 0.19 mg/m3 (≤ 0.03 ppm)	1	0.05	1.70 x 10-4
Drum Filling	≤ 0.19 mg/m3 (≤ 0.03 ppm)	1	0.025	8.48 x 10-3
			Total	1.95 x 10-3 mg/kg/day

Air sample was suctioned at the breathing zone of the worker at the suction rate of 0.4 L/min. for 5 min. and adsorbed through a collection can and analyzed by GC.

As shown in Table, the monitored exposure concentrations were below 0.19 mg/m3 at the drum filling work, the maintenance work and the sampling. The highest daily intake (respiratory EHEinh) for a worker (body weight; 70 kg, respiratory volume; 1.25 m3/hr) assigned to the drum filling work without protection is calculated as 1.70 x 10-3 mg/kg/day. The duration of dermal exposure is assumed to be 0.50 hrs/day. EHEder for the worker who implement all daily operation through hands is calculated as 7.50 x 10-2 mg/kg/day, assuming that the work is classified as non-dispersive, direct handling, and contact level is incidental.

Workers are recommended to wear protective gear such as a mask, rubber gloves and goggles to prevent exposure. Therefore EHEs are considered to substantially lower than the calculated value.

Source : Japan Industrial Safety and Health Association (JISHA), 2000
08.01.2002

Remark : Batch process.
Transesterification based on methyl methacrylate.
Purification by distillation.
Heavy ends : incineration.
Effluents : biological treatment plant.

Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
08.06.1994

Remark : Emissions during production and processing are low as the product is normally handled in closed systems. In the normal production process the substance is not released into the waste water or the air. Release into the waste water and the industrial sewage system during cleaning operations, processing, destillation is low < 1 t/year. Emissions to the air during those processes is well below 1 t/year.

Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
26.05.1997 (49)

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

1.11 Packaging

1.12 Possib. of Rendering Subst. Harmless

1.13 Statements Concerning Waste

1.14.1 Water Pollution

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)
Source : Roehm GmbH Darmstadt

EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

12.11.2001

1.14.2 Major Accident Hazards

Legislation	:	
Substance listed	:	no
No. in directive	:	
Source	:	Roehm GmbH Darmstadt EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

30.05.1994

1.14.3 Air Pollution

Classified by	:	other: Roehm GmbH
Labelled by	:	other: Roehm GmbH
Number	:	3.1.7 (organic substances)
Class of danger	:	III
Source	:	Roehm GmbH Darmstadt EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

09.01.2002

1.15 Additional Remarks

Remark	:	The product must be disposed of as special waste in accordance with regulations for special waste.
Source	:	Roehm GmbH Darmstadt EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

30.05.1994 (50)

1.16 Last Literature Search

1.17 Reviews

1.18 Listings e.g. Chemical Inventories

2.1 Melting Point

Value : = -30 °C
Sublimation :
Method : other: no data
Year :
GLP : no data
Test substance : no data
Source : HSDB (Hazardous substance data bank)
Flag : Critical study for SIDS endpoint
09.01.2002 (25)

Value : = -60 °C
Sublimation :
Method : other: no data
Year :
GLP : no
Test substance : other TS: source; not available
09.01.2002 (37)

Value : = -36 °C
Sublimation :
Method : other
Year :
GLP : no data
Test substance :
Remark : Beilstein 1998-1999
08.10.2001 (18)

Value : = -50 °C
Sublimation :
Method : other: not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

Value : = -30 °C
Sublimation :
Method : other: not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (24)

Value : <= -10 °C
Sublimation :
Method : other: no data
Year :
GLP :
Test substance : other TS: source; not available
09.01.2002 (12)

2.2 Boiling Point

Value	:	= 186 ° C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	source; not available
Source	:	Mitsubishi Gas Chemical Co., Inc.
10. 01. 2002		(11)

Value	:	= = 182 -190 ° C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
10.01.2002		(45)

Value	:	= 187 ° C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atochem Paris la Defens e EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
10.01.2002		(16)

Value	:	= 183 ° C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
10.01.2002		(40)

Value	:	= 186.3 ° C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Ullmann (1978) Ullmann's Encyclopaedie der technischen Chemie, Band 16: 609-614
10.01.2002		
Value	:	= 186.8 ° C at 1013 hPa
Decomposition	:	ambiguous
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Pavlov et al (1972) J. Appl. Chem. USSR (Engl. Transl.) 45, 623-624
10.01.2002		

2.3 Density

Type : density
Value : = .934 g/cm3 at 20° C
Method : other: no data
Year :
GLP : no data
Test substance : other TS: source; not available
Flag : Critical study for SIDS endpoint
09.01.2002 (12)

Type : density
Value : = .932 g/cm3 at 20° C
Method : other: no data
Year :
GLP : no data
Test substance : other TS: source; not available
09.01.2002 (37)

Type : density
Value : = .933 g/cm3 at 20° C
Method : other: not specified
Year :
GLP : no data
Test substance :
Remark : Vapour density: 6.54 kg/m3 at 20 degree C.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

Type : density
Value : = .93 g/cm3 at 25° C
Method : other: not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (26)

2.3.1 Granulometry

2.4 Vapour Pressure

Value : = 1.1 hPa at 25° C
Decomposition :
Method other (calculated)
Year : 1985
GLP : no
Test substance : other TS: source; not available
Source : SRC PhysProp Database
Flag : Critical study for SIDS endpoint
16.11.2001 (39)

Value : ≤ 1.33 hPa at 25° C
Decomposition :
Method

Year :
GLP : no data
Test substance : other TS: source; not available
09.01.2002 (12)

Value : = 1 hPa at 20° C
Decomposition :
Method other (calculated): not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

Value : = 5 hPa at 50° C
Decomposition :
Method other (calculated): not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

Value : = 13.3 hPa at 75° C
Decomposition :
Method other (calculated): not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (14)

2.5 Partition Coefficient

Log pow : = 1.13 at 25° C
Method OECD Guideline 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1997
GLP : yes
Test substance : other TS: source; Wako Pure Chemical Industries,Ltd, Purity; 99.9 %
Remark : After partition equilibrium of the test substance was established between n-octanol and water at three volume ratios, the concentrations of the test substance of both phase were determined with HPLC.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (12)

Log pow : = .3 at ° C
Method other (calculated)
Year :
GLP : no
Test substance :
Remark : Calculated according to Leo and Hansch (Freitexttype method).

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (30)

Log pow : = .6 at ° C
Method other (calculated)
Year :
GLP :
Test substance :
Remark : Calculated according to Rekker.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (46)

2.6.1 Water Solubility

Value : = 106.1 g/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH :
Method : other: no data
Year : 1996
GLP : no data
Test substance : other TS: source; no data
Source : SRC PhysPro Database
Flag : Critical study for SIDS endpoint
16.11.2001 (32)

Value : at ° C
Qualitative :
Pka : 8.44 at 25 ° C
PH : at and ° C
08.10.2001 (10)

Value : = 500 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : = 8 at and ° C
Method : other: not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (14)
Value : ≥ 100 g/l at ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method :
Year :
GLP : no data
Test substance : other TS: source not available
09.01.2002 (12)
Remark : Soluble in all proportions at 20 °C
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

2.6.2 Surface Tension

2.7 Flash Point

Value : ≥ 68.6 ° C
Type : closed cup
Method : other
Year :
GLP : no data
Test substance : other TS: source; not available
Flag : Critical study for SIDS endpoint
09.01.2002 (37)

Value : = 57 ° C
Type : other
Method : other: not specified
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002 (40)

Value : = 65 ° C
Type : open cup
Method : other
Year :
GLP : no data
Test substance :
Remark : Method: DIN 51 584 (A. PENSKY)
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002 (16)

Value : = 73.9 ° C
Type : other: no data
Method : other
Year :
GLP : no data
Test substance :
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002 (45)

Value : = 74 ° C
Type : closed cup
Method : other
Year :
GLP : no data
Test substance :
Remark : Method: DIN 51758
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002 (57)

2.8 Auto Flammability

Value	:	= 255 ° C
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

09.01.2002 (16)

2.9 Flammability

2.10 Explosive Properties

Result	:	other
Method	:	other: not speicfied
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Uncontrolled polymerization may occur to explosion
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

09.01.2002 (16)

2.11 Oxidizing Properties

2.12 Additional Remarks

Remark	:	Henry's constant : 3.144 10E -2 pa m3/mol Usually control the concentration of the additive and verify the clearness of the product 1 mg/m3 = 0.155 ppm 1 ppm = 6.431 mg/m3
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

09.01.2002 (16)

3.1.1 Photodegradation

Type	:	air
Light source	:	Sun light
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Conc. of subst.	:	at 25 ° C
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	500000 molecule/cm3
Rate constant	:	= 9.918E-11. cm3/(molecule*sec)
Degradation	:	= 50 % after 4 hour(s)
Deg. Product	:	
Method	:	other (calculated)
Year	:	
GLP	:	no
Test substance	:	
Result	:	Photodegradation is estimated as ca.4 hrs, employing the following calculation model. T1/2(photo air OH)=0.693/(9.918E-11 * 5.0E5)/3600
Source	:	SRC PhysProp Database
Flag	:	Critical study for SIDS endpoint

12.12.2001 (32)

3.1.2 Stability in water

Type	:	abiotic
t1/2 pH4	:	stable at 50 ° C
t1/2 pH7	:	= 4.5 day at 25 ° C
t1/2 pH9	:	= 3.3 hour(s) at 25 ° C
Deg. Product	:	
Method	:	OECD Guideline 111 "Hydrolysis as a Function of pH"
Year	:	1993
GLP	:	no data
Test substance	:	other TS
Deg. Product	:	108-01-0 203-542-8 2-dimethylaminoethanol 79-41-4 201-204-4 methacrylic acid
Method	:	-Preliminary Test a) Water Temperature: 50 ºC b) Nominal Concentration: ca. 100 mg/L c) pH: pH4 d) Number of Replicates: 2 e) Test Period: 5 days f) Exposure Vessel Type: Glass Vial -Final Test a) Water Temperature: pH7; 50, 60 70 ºC pH9; 30, 40 ºC b) Nominal Concentration: ca. 100 mg/L c) pH: pH7 and pH9 d) Number of Replicates: 2
Result	:	As a result of the preliminary test, 2-Dimethylaminoethyl methacrylate is not decomposed at pH4 and 50ºC in water after 5 days.
Test substance	:	source: Wako Pure Chemical Industries, LTD. purity: =99.9 %
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

09.01.2002 (12)

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Remark	:	The substance was reported to be unstabel in water at 20°C. At 80°C and an initial concentration of 0.48 mM complete hydrolysis to methacrylic acid and N,N -dimethylamino ethanol was observed. At pH 4 and temperatures between 20 and 70°C practically no hydrolysis was reported. Réf. : Kazantsev, O.A., Zilberman E.N., Salov V.N., Krasnov V.L.; Transformation of N,N-Dimethylaminoethylmethacrylate and acrylic acid in aqueous solutions ; Zh. Prikl. Khim. 60(9), 2142-2145 (1987).
Result	:	Hydrolysis of dimethylaminoethyl methacrylate, studied in 2.5% HCl at 25 and 40 degree C (96h) was found negligible. In 2.5% NaOH solution, at 25 degree C, 80% of the ester was hydrolysed within 25 minutes. Rate of alkaline hydrolysis of dimethylaminoethyl methacrylate in H2O and aq. EtOH decreased with increasing EtOH concentration (0-60%).The reaction was of the first order with respect to ester and the OH- ions.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

18.05.1994 (20) (21) (22)

3.1.3 Stability in soil

Type	:	other: hydrolysis
Radiolabel	:	
Concentration	:	
Soil temp.	:	degree C
Soil humidity	:	
Soil classif.	:	
Year	:	
Remark	:	The substance is expected to be susceptible to hydrolysis in particular in alkaline soils.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

18.05.1994

3.2 Monitoring data

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
Method	:	Distributions were calculated with following factors

2-Dimethylaminoethyl
molecular weight: 157.21
melting point [ºC]: -30
vapor pressure [Pa]: 110
water solubility [g/m3]: 106100
log Kow: 1.13
half life [h] in air: 4

in water: 110
in soil: 110
in sediment: 330
temp. [C]: 25

Result : The potential environmental distribution of MADAME obtained from a generic fugacity model Mackay level III under three emission scenarios is shown in Table. The results show that if MADAME is released into water, it is unlikely to migrate into other compartments. When MADAME is released to air, it is likely to be transported both to water and soil.

Compartment	Relese 100% to air	Relese 100% to water	Relese 100% to soil
Air	72.1%	0.0%	0.1%
Water	13.6%	99.7%	5.7%
Soil	14.2%	0.0%	94.2%
Sediment		0.0%	0.2%	0.0%

Flag : Critical study for SIDS endpoint
Source : Mitsubishi Gas Chemical Company, Inc., unpublished data

12.12.2001

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 1993
Result : Air : 1.09 %
Water : 98.86 %
Soil : 0.02 %
Sediment : 0.02 %
Suspended
Aquatic mat. : 0 %
Biota : 0 %
Fugacity : 4.44 10E7 Pa
Compound properties and parameters for calculation :
molecular weight : 157.2 g/mol
aqueous solubility : 510E5 g/m3
vapour pressure : 1 10E2 Pa
Henry's constant : 3.144 10E2 Pa m3/mol
log Pow : 0.45
Temperature : 20°C
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

18.05.1994

3.4 Mode of degradation in actual use

3.5 Biodegradation

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 20mg/l related to
related to
Contact time :
Degradation : = 95.3 % after 28 day
Result : readily biodegradable
Deg. Product :

Method	:	OECD Guideline 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1980
GLP	:	no data
Test substance	:	
Remark	:	Method: also EG-Richtlinie 84/449/EWG, Teil C.3 im EG-Amtsblatt L251, ISO 7824 (1984).
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Test condition	:	Concentration: 20 mg/l related to BOD.
Flag	:	Critical study for SIDS endpoint
09.01.2002		(47)

Deg. Product	:	yes
Method	:	
Year	:	
GLP	:	yes
Test substance	:	
Deg. Product	:	108-01-0 203-542-8 2-dimethylaminoethanol 79-41-4 201-204-4 methacrylic acid
Result	:	MADAME becomes Methacrylic acid (MAA) and 2-Dimethylaminoethanol (DMAE) by hydrolysis. Their biodegradation data are shown below. Methacrylic acid -Method: MITI (I) method (1974), corresponding to the OECD 301C (1981). -Test Substance: a)Degree of Purity: >=99.0% -Concentration: =100mg/L related to Test substance -Test Conditions: a)Water Temperature: 24-26 ºC b)Inoculum: standardized activated sludge, 30 mg/L assuspended solid c)Aeration: aerated by atmospheric air d)Exposure Vessel Type: 300 mL culture bottle e)Number of Replicate: 3 -Degradation: = 89-94% after 14 days (readily biodegradable) -Year: 1993 -Reference: CERI, Japan, Report No. 21114, Chemicals Evaluation and Research Institute, Japan, unpublished data. 2-Dimethylaminoethanol -Method: MITI (I) method (1974), corresponding to the OECD 301C (1981). -Concentration: =100mg/L related to Test substance -Degradation: = 60.5% after 14 days (readily biodegradable) -Year: 1976 -Reference: CERI, Japan, Chemicals Evaluation and Research Institute, Japan, unpublished data.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
10.01.2002		(11)

3.6 BOD5, COD or BOD5/ COD ratio

3.7 Bioaccumulation

3.8 Additional remarks

4.1 Acute/prolonged toxicity to fish

Type	:	semistatic
Species	:	*Oryzias latipes* (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	= 19.1
Method	:	OECD Guideline 203 "Fish, Acute Toxicity Test"
Year	:	1997
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries,Ltd., Purity 99.0 %, Lot No. WTL5063
Method	:	-Test Organisms: a) Size (length and weight): 2.1 cm (2.0 - 2.3 cm) in length; 0.13 g (0.10 - 0.20 g) in weight b) Age: Not described c) Any pretreatment: Acclimated for several days before testing, any groups showing > 5 % mortality were not used for testing. Not fed for 24 hours before the test started. d) Supplier/Source: SANKYO LAB SERVICE CO., LTD. (JAPAN) -Test Conditions: a) Dilution Water Source: Not described b) Dilution Water Chemistry: Not described c) Exposure Vessel Type: 3 L test solution in a 3 L Glass Beaker d) Nominal Concentrations (as mg/L): 0, 10, 18, 32, 56 and 100 e) Vehicle/Solvent and Concentrations: Not used f) Stock Solutions Preparations and Stability: No stock solution was prepared for the tests. The test substance was directly dissolved in 3 L-dilution water. g) Number of Replicates: 1 h) Fish per Replicates: 10 i) Renewal Rate of Test Water: Every 24 hours because the test substance is not stable in water j) Water Temperature: 23.0 - 25.0 ºC k) Light Condition: 16:8 hours, light-darkness cycle l) Feeding: No m) Water hardness: 30.3 mg/L
Method, cont.	:	- Analytical Procedure: The tested concentrations were measured at 0 hour and 24 hours (before exchange of test solution) by High Performance Liquid Chromatography method. -Statistical Method: a) Data Analysis: ProbitMethod for LC50 b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric Mean
Result		Measured Concentrations (as mg/L): 6.47, 10.8, 14.2, 23.0 and 35.0 after 24 h exposure (65 - 35 % of the nominal concentrations) Measured Concentration of MADAME during a 24-hour Exposure Test Condition (Fish, 96h)

Nominal Conc. mg/L	Measured Conc. (mg/L) 0 Hour new	24 Hour old	Geometric Mean	Percent of Nominal
Control	N.D.	N.D.	N.D.	
10	9.20	4.55	6.47	65
18	17.0	6.86	10.8	60
32	24.1	8.37	14.2	44
56	41.3	12.8	23.0	41
100	88.7	13.8	35.0	35

new: freshly prepared test solutions
old: test solutions after 24 hours exposure period

- Water chemistry in test (pH and DO): pH 7.22- 7.61 (control), DO 5.31 - 8.70 mg/L

-Effect Data(mortality):
96hr LC50 =19.1mg/L (95% Confidence Interval:15.8-23.5mg/L)

- Cumulative Mortality:

Nominal Concentration mg/L	Cumulative N umber of Dead 24hr	48hr	72hr	96hr
Control	0	0	0	0
10	0	0	0	0
18	0	0	1	1
32	0	0	1	2
56	3	3	4	6
100	10	10	10	10

Result, cont. : -Other Effect

Symptom of Toxicity Observed in Orange killfish (*Oryzias latipes*)

Nominal Concentration mg/L	Symptom 24hr	48hr	72hr	96hr
Control	Normal	Normal	Normal	Normal
10	Normal	Normal	Normal	Normal
18	Normal	Normal	Normal	Normal
32	Convulsion Rolling	Convulsion	Convulsion	Rolling
56	Convulsion Rolling	Convulsion	Convulsion	Normal
100	All dead			

- Calculation of toxic values: Based on the measured concentrations, because the measured concentrations were < 80 % of the nominal concentrations

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (38)
Type : semistatic
Species : *Oryzias latipes* (Fish, fresh water)
Exposure period : 14 day
Unit : mg/l

Analytical monitoring : yes
LC0 : = 1.36
LC50 : = 5.26
Method : OECD Guideline 204 "Fish, Prolonged Toxicity Test: 14-day Study"
Year : 1997
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries,Ltd., Purity 99.0 %, Lot No. WTL5063

Method

-Test Organisms:
a) Size (length and weight): 2.12 cm (2.0 - 2.3 cm) in length; 0.122 g (0.101 - 0.152 g) in weight
b) Age: Not described
c) Any pretreatment: Acclimated for several days before testing, any groups showing > 5 % mortality were not used for testing. Not fed for 24 hours before the test started.
d) Supplier/Source: SANKYO LAB SERVISE CO., LTD. (JAPAN)

-Test Conditions:
a) Dilution Water Source: Not described
b) Dilution Water Chemistry: Not described
c) Exposure Vessel Type: 5 L test solution in a 5 L-Glass Beaker
d) Nominal Concentrations (as mg/L): 0, 2.2, 4.6, 10, 22 and 46
e) Vehicle/Solvent and Concentrations: Not used
f) Stock Solutions Preparations and Stability: No stock solution was prepared for the tests. The test substance was directly dissolved in 5 L-dilution water.
g) Number of Replicates: 1
h) Fish per Replicates: 10
i) Renewal Rate of Test Water: Every 24 hours because the test substance is not stable in water
j) Water Temperature: 23.0 - 25.0 ºC
k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: No
m) Water hardness: 30.3 mg/L

- Analytical Procedure: The tested concentrations were measured at 0 hour, 7 days and 13 days (after exchanges of the test solution, and after 24 hours) by High Performance Liquid Chromatography method.
-Statistical Method:
a) Data Analysis: Probit Method for LC50
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean measured concentration during 14 days

Result

- Measured Concentrations (as mg/L): 1.36, 2.96, 5.86, 10.1 and 21.0 (Time-weighted Mean during 14 days, 62 - 46 % of the nominal concentrations)

Measured Concentration of MADAME during a 24-hour Exposure Test Condition (Fish, 14d)

Nominal Conc. mg/L	Measured Conc. (mg/L) 0 day new	0 day old	1 day new	1 day old	Percent of Nominal
Control	N.D.	N.D.	-----	----.	
2.2	1.87	1.05	85	48	
4.6	4.57	2.15	99	47	
10	10.0	4.16	100	42	
22	18.1	6.19	82	28	
46	46.4	8.64	101	19	

Nominal Conc. mg/L	Measured Conc. (mg/L) 7 day new	7 day old	8 day new	8 day old
Control	N.D.	N.D.	-----	----.
2.2	1.81	0.97	82	44
4.6	4.23	1.99	92	43
10	9.36	3.07	94	31
22	18.7	4.28	85	19
46	44.7	6.19	97	13

Nominal Conc. mg/L	Measured Conc. (mg/L) 13 day new	13 day old	14 day new	14 day old
Control	N.D.	N.D.	-----	----.
2.2	1.73	0.98	79	45
4.6	3.95	1.75	86	38
10	9.16	2.68	92	27
22	19.3	3.73	88	17
46	-----	-----	----	----

Result, cont. :

Nominal Conc. mg/L	Time-weighted Mean during14 day mg/L
Control	-----.
2.2	1.36
4.6	2.96
10	5.86
22	10.1
46	20.0

new: freshly prepared test solutions
old: test solutions after 24 hours exposure period

- Water chemistry in test (pH and DO): pH 7.27 - 7.80 (control), pH 7.58 - 8.80 (46 mg/L), DO 5.31 - 8.70 mg/L

-Effect Data(mortality)
14 days LC50 = 5.26mg/L(95% Confidence Interval:13.87-7.03 mg/L)
14 days LC0 = 2.96mg/L

- Cumulative Mortality:

Nominal concentration mg/L	Cumulative Number of Dead 1d	2d	3d	4d	5d	6d	7d	8d	9d	10d	11d	12d	13d	14d
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4.6	0	0	0	0	0	0	0	0	0	0	0	1	2	2
10	1	1	1	1	2	2	2	2	2	3	5	5	5	5
22	1	1	2	4	5	5	6	7	7	8	8	9	9	9
46	7	8	9	9	9	9	9	10	10	10	10	10	10	10

-Other Effect
Symptom of Toxicity Observed in Orange killfish (*Oryzias latipes*)

Result, cont.

Nominal Concentration mg/L | Symptom 0d | 7d | 10d | 14d

Control	Normal	Normal	Normal	Normal
2.2	Normal	Normal	Normal	Normal
4.6	Normal	Normal	Normal	Normal
10	Normal	Anorexia dull behavior	Anorexia	Aorexia
22	Convulsion (light)	Anorexia dull behavior	Anorexia dull behavior	Anorexia dull behavior
46	Convulsion Dead(6 fishes)	Anorexia dull behavior	all dead	

Mean Fish Weight and Length (14 days)

Nominal Concentration mg/L	weight(mg/L)	length(mm)
Control	126.9	21.3
2.2	138.5	21.8
4.6	118.6	21.1
10	139.0	22.8
22	174	24.0
46	-	-

- Calculation of toxic values: Based on the measured concentrations, because the measured concentrations were < 80 % of the nominal concentrations

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (38)

Type :
Species : other: Osteichtyes (Common Name: Bony fish superclass)
Exposure period : 72 hour(s)
Unit : mg/l
Analytical monitoring :
LC50 : = 150
Method :
Year : 1975
GLP :
Test substance :
11.12.2001 (1)

Type :
Species : *Carassius auratus* (Fish, fresh water)
Exposure period : 72 hour(s)
Unit : mg/l
Analytical monitoring : no data
LC50 : = 139.5
Method : other
Year :
GLP : no data
Test substance : no data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

08.12.1993 (43)

Type	:	
Species	:	*Leuciscus idus* (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	
LC0	:	= 300
LC50	:	= 331 - 592
LC100	:	= 600
Method	:	other
Year	:	
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: DIN 38412, Teil 15.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

11.12.2001 (51)

4.2 Acute toxicity to aquatic invertebrates

Type	:	semistatic
Species	:	*Daphnia magna* (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	= 18.7
EC50	:	= 33
Method	:	OECD Guideline 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year	:	1997
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries,Ltd., Purity 99.0 %, Lot No. WTL5063
Method	:	- Test Organisms: a) Age: < 24 hours old b) Supplier/Source: National Institute for Environmental Studies (JAPAN) - Test Conditions: a) Dilution Water Source: Not described b) Dilution Water Chemistry: Not described c) Exposure Vessel Type: 100 mL test solution in a 100 mLGlass Beaker d) Nominal Concentrations (as mg/L): 0, 18, 32, 56, 100, 180 and 320 e) Vehicle/Solvent and Concentrations: Not used f) Stock Solutions Preparations and Stability: For 320 mg/L and 180 mg/L test concentrations, the test substance were dissolved in each 100 mL-dilution water. For other test concentrations, 1.0 % stock solution was prepared. g) Number of Replicates: 4 h) Individuals per Replicates: 5 i) Renewal Rate of Test Water: Every 24 hours because the test substance is not stable in water j) Water Temperature: 19.7 - 20.0 ºC k) Light Condition: 16:8 hours, light-darkness cycle l) Feeding: No m) Water hardness: 30.3 mg/L - Analytical Procedure: The tested concentrations were measured at 0 hour

and 24 hours (before exchanges of the test solution) by High Performance Liquid Chromatography method.

- Statistical Method:
a) Data Analysis: Probit Method for EC50
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric Mean

Remark : NOEC was determined based on immobility.

Result : - Measured Concentrations (as mg/L): 10.5, 18.7, 29.7, 43.7, 70.4 and 119 (58 - 37 % of the nominal concentrations)

Measured Concentration of MADAME during a 24-hour Exposure Test Condition (*Daphnia magna*, 48h)

Nominal Conc. mg/L	Measured Conc. (mg/L) 0 Hour new	24 Hour old	Geometric Mean	Percent of Nominal
Control	N.D.	N.D.	N.D.	
18	15.0	7.33	10.5	58
32	30.1	11.6	18.7	58
56	51.7	17.0	29.7	53
100	76.2	25.0	43.7	44
180	145	34.2	70.0	39
320	285	49.4	119	37

- Water chemistry in test (pH and DO): pH 7.52 - 7.67 (control), DO 8.43 - 8.93 mg/L
-Effect Data(immobilization):
48hr EC50 = 33mg/L
48hr NOEC = 18.7mg/L
Cumulative Number of Immobilized Parental Daphnia

Nominal Concentration mg/L	Cumulative Number of Immobilized Daphnia magna 24hr	48hr
Control	0	0
18	0	0
32	0	0
56	0	4
100	6	20
180	12	20
320	20	20

the values including dead *Daphnia magna*

- Calculation of toxic values: Based on the measured concentrations, because the measured concentrations were < 80 % of the nominal concentrations.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

09.01.2002 (38)

Type :

Species : *Daphnia magna* (Crustacea)

Exposure period : 48 hour(s)

Unit : mg/l

Analytical monitoring : no

EC50 : = 53

Method : ISO 6341 15 "Water quality - Determination of the inhibition of the mobility of *Daphnia magna* Straus (Cladocera, Crustacea)"

Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	EC(I)50, 24 h = 73 mg/l
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

08.12.1993 (15)

4.3 Toxicity to aquatic plants e.g. algae

Species	:	*Selenastrum capricornutum* (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	= 18
EC50	:	= 41.6
Method	:	other: OECDGuideline 201
Year	:	1997
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries,Ltd., Purity 99.0 %, Lot No. WTL5063
Method	:	- Test Organisms: a) Method of Cultivation: Subculturing in OECD medium until use b) Stain Number: Not described c) Supplier/Source: Not described - Test Conditions: a) Medium: OECD medium b) Exposure Vessel Type: 100 mL Medium in a 300 mL Conical Flask c) Nominal Concentrations (as mg/L): 0, 10, 18, 32, 56 and 100 d) Vehicle/Solvent and Concentrations: Not used. e) Stock Solutions Preparations and Stability: The concentration of the test substance in the stock solution was 10,000 mg/L. f) Number of Replicates: 3 g) Initial Cell Number: 10,000 cells/mL h) Water Temperature: 22.8 - 23.2 ºC i) Light Condition: 4,000 - 5,000 lux, continues m) Water hardness: 30.3 mg/L - Analytical Procedure: The tested concentrations were measured at the start (0 hour) and the end (72 hours) of the tests by High Performance Liquid Chromatography method. - Statistical Method: a) Data Analysis: Not described b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Not calculated
Remark	:	NOEC was determined based on growth inhibition. The hydrolysis rate is extremely large at higher pH (half life: 4.54days at pH7 and 3.31 hours at pH9). MADAME is hydrolyzed to Methaclylic acid (MAA) and 2-Dimethylaminoethanol (DMAE). There is some possibility of effects of MAA or DMAE instead of MADAME on the aquatic organisms.
Result	:	Measured Concentrations (as mg/L): 72 hours; N.D., 0.07, 0.30, 0.86 and 2.18 (0.39 - 2.18 % of nominal concentrations) Measured Concentration during a 72-hour exposure to

Selenastrum capricornutum

Nominal Conc. mg/L	Measured Conc. (mg/L) 0 Hour	Percent of Nominal	72 Hour	Percent of Nominal
Control	N.D.	.	N.D.	
10	8.82	88.2	N.D.	-----
18	15.2	84.4	0.07	0.39
32	25.9	80.9	0.30	0.94
56	48.3	86.3	0.86	1.54
100	83.4	83.4	2.18	2.18

- Water chemistry in test (pH and DO): pH 9.03 - 9.25 at the start of the test, pH 7.90 - 9.13 at the end of the test
-Effect Data:
area method
EbC50(0-72hr) = 41.6mg/L (95% Confidence Interval: 37.3-46.5mg/L)
NOEC = 18mg/L
rate method
ErC50(24-48hr) = 69.7mg/L (95% Confidence Interval: 57.1-85.1mg/L)
NOEC = 56mg/L
ErC50(24-72hr) = 84.0mg/L (95% Confidence Interval: 74.5-94.8mg/L)
NOEC = 32mg/L
- Mean Cell Concentration of Each Flask (as cells/mL)

Nominal Concentration mg/L	Cell density of *Selenastrum capricornutum* Cell Density (x 10,000 cells/mL) 0hr	24hr	48hr	72hr
Control	1.0	3.6	18.7	81.6
10	1.0	3.5	15.2	83.9
18	1.0	4.0	16.3	80.3
32	1.0	2.8	12.8	53.7
56	1.0	2.3	6.6	30.2
100	1.0	1.0	0.361	2.9

- Growth Curves: Log phase during the test period

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (38)

4.4 Toxicity to microorganisms e.g. bacteria

Type : aquatic
Species : *Pseudomonas putida* (Bacteria)
Exposure period : 18 hour(s)
Unit : mg/l
Analytical monitoring : no data
EC10 : = 42.7
Method : other
Year :
GLP : no data
Test substance :

Remark : Method: Bringmann-Kuehn.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

10.01.2002 (48)

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
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	= 4.35
EC50	:	= 7.86
LC50	:	= 16.6
Method	:	other: OECD Guideline 211
Year	:	1997
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries,Ltd., Purity 99.0 %, Lot No. WTL5063
Method	:	- Test Organisms: a) Age: < 24 hours old b) Supplier / Source: National Institute for Environmental Studies (JAPAN) - Test Conditions: a) Dilution Water Source: Not described b) Dilution Water Chemistry: Not described c) Exposure Vessel Type: 80 mL test solution in a 100 mL Glass Beaker d) Nominal Concentrations (as mg/L): 0, 0.632, 2.0, 6.32, 20 and 63.2 e) Vehicle/Solvent and Concentrations: Not used f) Stock Solutions Preparations and Stability: 1.0% stack solution was prepared. g) Number of Replicates: 10 h) Individuals per Replicates: 1 i) Renewal Rate of Test Water: Every 24 hours because the test substance is not stable in water j) Water Temperature: 20.4 - 21.0 ºC k) Light Condition: 16:8 hours, light-darkness cycle, not more than 1,200 lux l) Feeding: 0.18 mg carbon/day/individual (Chlorella Vulgaris) m) Water hardness: 30.3 mg/L - Analytical Procedure: The tested concentrations were measured before and after renewal of the test water by High Performance Liquid Chromatography method. Total of 8 times were measured during the test period. - Statistical Method: a) Data Analysis: Probit Method for LC50, Logit Method for EC50 b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean measured concentration during 21 days
Remark	:	NOEC was determined based on the cumulative number of juveniles produced per adult alive for 21 days.
Result	:	Effect: reproduction - Measured Concentrations (as mg/L): 0.479, 1.44, 4.35, 11.2 and 33.8 (76 - 54 % of the nominal concentrations) Measured Concentration of MADAME during a 21-day Exposure of *Daphnia magna* under Semi-Static Test Condition

Nominal Conc. mg/L	Measured Conc. (mg/L) 0 day new	0 day old	1 day new	Percent of Nominal 1 day old
Control	N.D.	N.D.	-----	----.
0.632	0.695	0.343	110	54
2.0	1.90	0.97	95	49
6.32	6.14	2.79	97	44
20	14.6	6.07	73	30
63.2	60.0	16.9	95	27

Nominal Conc. mg/L	Measured Conc. (mg/L) 7 day new	7 day old	8 day new	Percent of Nominal 8 day old
Control	N.D.	N.D.	-----	----.
0.632	0.641	0.350	101	55
2.0	1.83	1.02	92	51
6.32	5.96	2.92	94	46
20	16.1	7.07	81	35
63.2	58.3	17.2	92	27

Nominal Conc. mg/L	Measured Conc. (mg/L) 14 day new	14 day old	15 day new	Percent of Nominal 15 day old
Control	N.D.	N.D.	-----	----.
0.632	0.583	0.383	92	61
2.0	1.98	1.14	99	57
6.32	6.08	3.16	96	50
20	18.6	7.31	93	37
63.2	-----	------	-----	-----

Nominal Conc. mg/L	Measured Conc. (mg/L) 20 day new	20 day old	21 day new	Percent of Nominal 21 day old
Control	N.D.	N.D.	-----	----.
0.632	0.582	0.359	92	57
2.0	1.94	1.09	97	55
6.32	6.15	3.04	97	48
20	18.3	7.15	92	36
63.2	-----	------	-----	-----

Result, cont.

Nominal Conc. mg/L	Time-weighted Mean during14 day mg/L
Control	-----.
0.632	0.479
2.0	1.44
6.32	4.35
20	11.2
63.2	33.8

new: freshly prepared test solutions
old: test solutions after 24 hours after freshly prepared

- Water chemistry in test (pH and DO): pH 7.63 - 7.74 (control), pH 8.70 - 8.83 (63.2 mg/L), DO 7.56 - 8.70 mg/L, Hardness 29.5 - 39.3
-Effect Data(reproduction):
21days LC50 = 16.6mg/L (parental mortality)

21days EC50 = 7.86mg/L
21days NOEC = 4.35mg/L

- Cumulative Number of Dead Parental Daphnia

Nominal Concentration mg/L	Cumulative Number of Dead Parental Daphnia 1d	7d	14d	21d
Control	0	0	0	0
0.632	0	0	0	0
2.0	0	0	0	0
6.32	0	0	0	0
20	0	0	0	0
63.2	0	9	10	10

- Time (days) of the First Production of Young: Mean; Control (11.2), 0.632 mg/L (11.3), 2.0 mg/L (12.1), 6.32 mg/L (11.7), 20 mg/L (11.8) and 63.2 mg/L (-)

- Cumulative numbers of juveniles produced per adult alive for 21 days

Result, cont.

Vessel No.	Control, (Measured Concentration, mg/L)	Nominal concentration, mg/L 0.632 (0.479)	2.0 (1.44)	6.32 (4.35)	20 (11.2)	63.2 (33.8)	
1	63	61	44	56	16		D
2	66	62	47	71	19		D
3	82	68	77	70	6		D
4	59	84	61	66	1		D
5	83	85	48	65	3		D
6	74	61	70	48	9		D
7	65	68	63	49	11		D
8	71	60	54	80	4		D
9	50	76	55	44	2		D
10	65	51	53	72	–		D
Mean	67.8	67.6	57.2	62.1	7.9		–
S.D.	10.1	11.0	10.5	12.1	6.4		–
Signifucant ratio				*	*		

D: Were not calculated because the parental *Daphnia magna* was dead during a 21-days testing period.

*1: Indicate a significant difference by Dunnett mulitiple comparioson procedure

- Calculation of toxic values: Based on the measured concentrations, because some data of the measured concentrations were < 80 % of the nominal concentrations.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (38)

4.6.1 Toxicity to soil dwelling organisms

4.6.2 Toxicity to terrestrial plants

4.6.3 Toxicity to other Non-Mamm. terrestrial species

Species	:	other: *Agelais Phoenicus*
Endpoint	:	mortality
Exposure period	:	18 hour(s)
Unit	:	mg/kg bw
LD50	:	= 98
Method	:	other
Year	:	
GLP	:	
Test substance	:	
Remark	:	Repellency value (R50)= 1.0
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Test condition	:	Method: wild-trapped birds were preconditionned to captivity for 2 to 6 weeks and were usually dosed by gavage with solutions or suspensions of the test chemical in propylene glycol, according to methods described by DeCino et al. (1966), Schafer (1972) and Schafer et al. (1967). LD50 values were calculated by the method of Thompson (1948), Thompson and Weil (1952) and Weil (1952). Repellency tests were conducted by the methods of starr et al. (1964) and Schafer and Brunton (1971), and R50's were calculated either by the method of Litchfield and Wilconxin (1949) or Thompson and weil (1952). Bird species: *Agelaius phoeniceus* (Red-winged blackbird).

10.01.2002 (56)

4.7 Biological effects monitoring

4.8 Biotransformation and kinetics

4.9 Additional remarks

5.1.1 Acute oral toxicity

Type	:	LD50
Species	:	rat
Strain	:	Crj: CD(SD)
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: Corn Oil
Value	:	> 2000 mg/kg bw
Method	:	OECD Guideline 401 "Acute Oral Toxicity"
Year	:	1998
GLP	:	yes
Test substance	:	other TS: 99.9% purity, Sanyo-Kasei Co.
Remark	:	There were no deaths of animals in the 2000 mg/kg dosed group. At necropsy, raised patches in the forestomach were observed in males of the 2000 mg/kg group. Histopathologically, papillomatous hyperplasia in the forestomach was apparent.
Result	:	A single oral toxicity test revealed an LD50 value of above 2000 mg/kg bw for this chemical in both sexes.
Test condition	:	Doses; 0 (vehicle), 500, 1000, 2000 mg/kg bw. Vehicle; Corn oil. Administration; One administration Number of animals: 5 males/5 females Observation period; 14 days
Source	:	MHW, Japan: 1998
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

12.12.2001 (33)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 1751 mg/kg bw
Method	:	other: not specified
Year	:	1982
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.01.2002 (23)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 2659 mg/kg bw
Method	:	other: not specified
Year	:	1978
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Density: 0.933 g/cm3
Source	:	Roehm, EUROPEAN COMMISSION- European Chemicals Bureau Ispra(VA)

09.01.2002 (54)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 1550 mg/kg bw
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

09.01.2002 (27)

5.1.2 Acute inhalation toxicity

Type	:	LC50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Exposure time	:	4 hour(s)
Value	:	= .62 mg/l
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.01.2002 (23)

Type	:	LC50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Exposure time	:	2 hour(s)
Value	:	= 1.8 mg/l
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.01.2002 (23)

5.1.3 Acute dermal toxicity

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	undiluted

Value	:	> 2000 mg/kg bw
Method	:	OECD Guideline 402 "Acute dermal Toxicity"
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Within 72 hrs of application of the test substance, hypokinesia, sedation and dyspnea were observed. Local signs of marked irritations were noted during the study. The body weight gain of the animals was not influenced by the treatment. No deaths occured at the dose level of 2000 mg/kg. The macroscopic exa mination revealed no abnormalities in the animals sacrificed at the end of the study. Signs of cutaneous irritation had eversed.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test condition	:	The test subs tance was applied in its original form directly to the skin of test animals at a dose level of 2000 mg/kg. After 24 hrs under semi-occlusive dressing, no residual test substance was observed.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

09.01.2002 (2)

Type	:	LD50
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 3000 mg/kg bw
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

09.01.2002 (27)

5.1.4 Acute toxicity, other routes

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 97 mg/kg bw
Method	:	other
Year	:	1973
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

10.01.2002 (28)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	

Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 310 mg/kg bw
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.01.2002 (42)

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 25 mg/kg bw
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.01.2002 (41)

5.2.1 Skin irritation

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	24 hour(s)
Number of animals	:	4
PDII	:	8
Result	:	corrosive
EC classification	:	corrosive (causes burns)
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Severe erythema, oedema and necrosis were exhibited 24 hrs following application. Reactions persisted to 72 hrs. For all animals and for both of intact skin and abraded skin, maximum score of 4 was marked in the erythema and oedema rating, therefore a Primary Irritation Score of 8 was obtained.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Test condition	:	The method described in the Federal Hazardous Substances Labelling Act Regulations, Section 191.11, published in the Federal Register - 29 F.R. 13009, 1964. A 0.5 mL sample of the test material was applied to areas of intact and abraded areas of skin. These areas were then occuluded with square surgical gauge patches, each measuring 1 inch x 1 inch. After 24 hrs exposure, the patches were removed and the resulting reactions evaluated. The valuation was done again at 72 hrs.

Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
09.01.2002		(8)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	highly irritating
EC classification	:	irritating
Method	:	Draize Test
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Draize index 5.9 of 8 (reevaluated according to OECD 404)
Source	:	Roehm, EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002		(53)

Species	:	guinea pig
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	highly irritating
EC classification	:	irritating
Method	:	other: no data
Year	:	1997
GLP	:	no data
Test substance	:	no data
Remark	:	Irritation occurs even when using a silicon or 5%Zn cream.
Source	:	Roehm, EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.01.2002		(53)

5.2.2 Eye irritation

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	2 hour(s)
Comment	:	
Number of animals	:	2
Result	:	corrosive
EC classification	:	irritating
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Despite the rinsing treatment severe corneal, iris and conjunctival lesions were displayed by both animals within 2 hrs of instillation. The test was terminated at this point. It is reasonable to assume that similar levels of injury would be produced if full scale testing were conducted, and that the product would be classified as corrosive to the eye.

Animal No.	Time (hrs)	Cornea Redness	Iris	Conjunctivae Chemosis		
5.		2	3	2	3	3
6.		2	4	2	3	4

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

Test condition : The method described in the Federal Hazardous Substances Labelling Act Regulations, Section 191.11, published in the Federal Register - 29 F.R. 13009, 1964.
0.1 mL of the test substance was instilled into one eye of each animal. The lids were gently held togather for one second and the eye was then rinsed with 20 mL lukewarm water at 4 seconds after instillation. The eyes were examined 2 hrs after instillation.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

09.01.2002 (8)

5.3 Sensitization

Type : Guinea pig maximization test
Species : guinea pig
Number of animals : 30
Vehicle : injectable isotonic solution of 0.9% NaCl
Result : not sensitizing

Classification : not sensitizing
Method : OECD Guideline 406 "Skin Sensitization"
Year : 1991
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Remark : The general behaviour and the body weight gain of the animals were not influenced by the treatment. After the challenge cutaneous application of the test substance, a very slight erythema (score 1) was observed on the right flank of 16 out of 20 treated animals. As the cutaneous reactions were very slight and the reactions observed at the 24 hrs scoring period were reversible at the 48 hrs scoring period, the cutaneous reactions were attributed to orthoergique reaction. No cutaneous reactions lilely to be caused by the sensitization potential of this test substance (MADAME) were observed.

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

Test condition : Test animals were 30 Dunkin Hartley guinea pigs (15 males and 15 females) and were allocated to two groups. 10 animals (5 males and 5 females) were in the negative control group and 20 animals (10 males and 10 females) were in the treatment group by MADAME.

Test periods were as follows:
[Induction period] 10 days during this period, the animals were treated with the vehicle(control group) or the test substance(treated group) as explained below.
On day 1, 0.1 mL of the test substance was administered by intradermal route at a concentration of 1 % in an isotonic solition of 0.9 % NaCl.On day 8, 0.5 mL of the test substance at a concentration of 25 % was applied by cutaneous route.
[Period without treatment] 12 days
[Challange test] 24 hrs
A challenge cutaneous application of 0.5 mL of the vehide (left flank) and 0.5 mL of the test substance at a concentration of 5 % in the vehicle (right

flank) were performed on all animals. The substances were held in place for 24 hours by means of an occlusive dressing.
[Examination]
The cutaneous reactions were evaluated at the challenge application site, 24 and 48 hrs after removal of the dressing. After the final scoring period, the animals were sacrificed and cutaneous samples were taken from the challenge application sites in all animals. Due to the absence of doubtful macroscopic cutaneous reactions, no histological examination was performed on the cutameous samples.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (9)

5.4 Repeated dose toxicity

Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	Males, 43 days Females, from 14 days before mating to day 3 of lactation (41-52 days)
Frequency of treatment	:	once daily
Post obs. period	:	1 day
Doses	:	0(vehicle), 40, 200, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 200 mg/kg bw
Method	:	OECD combined study TG422
Year	:	1998
GLP	:	yes
Test substance	:	other TS: 99.9% purity, Sanyo-Kasei Co.
Result	:	The NOAELs for repeat dose toxicity are considered to be 200 mg/kg/day for both sexes. [Males] At 1000 mg/kg/day, no death was occured. *By the observation, late onset of twitching, chronic convulsion and suppression of body weight gain were observed. *By the histopathological examination: Degeneration of nerve fibers in the brain and spinal cord, hyperplasia of the mucosa, edema and inflammatory cell infiltration in the forestomach,and increased kidneys' weight and livers's weight without histopathological changes were revealed. *By the hematological and blood chemical examination: Slight increse in BUN and slight anemic changes such as decreases in erythrocyte counts, hemoglobin concentration and hematocrit value, associated with a significant increase in reticulocyte ratio were revealed. At 200 mg/kg/day, no adverse effects except for slight anemic changes such as decrease in hemoglobin concentration and hematocrit value with increase in reticulocyte ratio were obs erved. However, the severities of this slight anemic changes were considered toxicologically insignificant.At 40 mg/kg/day, no effects were observed. [Females] At 1000 mg/kg/day, 3 females out of 12 died. *By the observation, late onset of twitching, chronic convulsion, suppression of body weight gain and a decrease in food consumption in lactation period were observed.

*By the histopathological examination, the degeneration of nerve fibers in the brain and the spinal cord, and the hyperplasia of the mucosa in gastric tract,the edema and inflammatory cell infiltration in the forestomach, and the atrophy of thethymus were revealed.
Also the increases in the weight of the kidney and the adrenals without histopathological changes were observed.

At 200 mg/Kg/day and 40 mg/kg/day, no effects were observed.

Result, cont.

The results of the blood examination in male rats are summarized below.

Hematological examination results in male rats

Dose (mg/kg)	0	200	1000
No. of animals	12	12	11
RBC *(10000/uL)*	881.7 ± 43.6	859.8 ± 36.7	821.6 ± 34.1**
Hematocrit %	46.73 ± 2.45	44.84 ± 1.26*	41.72 ± 1.97**
Hemoglobin g/dL	15.91 ± 0.69	15.28 ± 0.40*	14.24 ± 0.74**
Reticulocyte ‰	17.81 ± 2.61	21.56 ± 3.57*	24.84 ± 3.75**

Values are expressed as Mean ± S.D.
Significantly different from control: * P<0.05 ** P<0.01

The major histopathological findings in rats are summarized below. Major histopathological findings in rat.

[Male]

Dose (mg/kg)		0	200	1000
# of animals		12	12	11
Findings in Stomach				
Dilatation, gasteric gland.	+	0	0	0
Edema.	+	0	0	7**
Hyperplasia, squamous, forestomach diffuse.	+	0	0	11**
Inflammatory cell infiltration, forestomach.	+	0	0	10**
Ulcer, forestomach.	+	0	0	0
Ulcer, glandular stomach	+	0	0	0
Findngs in Brain				
Degeneration, nerve fiber	+	0	0	3
Spinal cord				
Degeneration, nerve fiber	+	0	0	8**

Result, cont.

[Female]

Scheduled sacrifice		Dead				
Dose (mg/kg)		0	200	1000	0	1000
Number of animals		11	12	9	1 a)	3 b)
Findimgs in Stomach						
Dilatation, gasteric gland.	+	0	0	0	0	0/2
Edema.	+	0	0	2	0	1/2
Hyperplasia, squamous, forestomach diffuse.	+	0	0	9**	0	2/2
Inflammatory cell infiltration, forestomach.	+	0	0	5**	0	1/2
Ulcer, forestomach.	+	0	0	1	0	0/2
Ulcer, glandular stomach	+	0	0	0	0	1/2
Findngs in Brain						
Degeneration, nerve fiber	+	0	0	4	0	0
Spinal cord						
Degeneration, nerve fiber	+	0	0	6**	0	0

Note: + Slight
** Significantly different from control: P< 0.01
a) One animal died of dystocia at 23 of gestation
b) Dead animals were observed at 26 and 38 days after commencement of administration.

Source : MHW, Japan: 1998

Test condition : Number of animals/group: Males, 12; females, 12

As the LD50 value of > 2000 mg/kg was known, a preliminary test to decide the highest dose level at 30, 100, 300, and 1000 mg/kg/day for 14 days was conducted. At 1000 mg/kg/day, decrease of body weight in males and suppression of body weight increase in females were observed. Then the highest dose level for the test was set at 1000 mg/kg/day.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

10.01.2002 (33)

Species : rat
Sex : male/female
Strain : other: Alderly Park (SPF)
Route of admin. : inhalation
Exposure period : 3 weeks
Frequency of treatment : 6 h/day; 5 d/week
Post obs. period : no
Doses : 15 x 100 ppm or 15 x 250 ppm (Vapour concentration)
Control group : no data specified
NOAEL : = 100 ppm
LOAEL : = 250 ppm
Method : other: not specified
Year : 1970
GLP : no data

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Strain: Aderly-Park (SPF) 4 males and 4 females in each group. Whole body exposure. The substance is introduced by a constant-flow pump.
Result	:	At 250 ppm: Nose and eye irritation, heavy breathing, increase of body weight is slow. No change of heamtological and clinical parameters. No pathological (macroscopical and microscopical) effect on organs is observed. At 100 ppm: No toxic effect is observed.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra(VA)
Reliability	:	(2) valid with restriction
Flag	:	Critical study for SIDS endpoint
10.01.2002		(17)

Species	:	rabbit
Sex	:	no data
Strain	:	no data
Route of admin.	:	dermal
Exposure period	:	7 days
Frequency of treatment	:	twice per day
Post obs. period	:	7 days
Doses	:	30 uL on sheared skin (25 % to 35 % in solution)
Control group	:	yes
Method	:	other: not specified
Year	:	1990
GLP	:	no data
Test substance	:	no data
Result	:	Important morphological change (coagulation, necrosis, oedema and little cell infiltration of the derm). Highly irritation due to 2-propenoic acid, 2-methyl, dimethylaminoethylester is not reversible 7 days after the end of treatment. Systemic effects were not reported.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
10.01.2002		(31)

5.5 Genetic toxicity 'in vitro'

Type	:	Bacterial reverse mutation assay
System of testing	:	*Salmonella typhimurium* TA100, TA1535, TA98, TA1537, *Escherichia coli* WP2uvr A
Concentration	:	[Confirmation test for the positive results of the trial tests] -S9 mix.; 1000,1500,2000, 2500, 3000, 3500, 4000, 4500, 5000
Cycotoxic conc.	:	More than 3500 ug/plate (TA98, TA1537) without S9 mix in the confirmation tests
Metabolic activation	:	with and without
Result	:	positive
Method	:	Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year	:	1998
GLP	:	yes
Test substance	:	other TS: 99.9% purity, Sanyo Kasei Co.
Result		The result was positive because the chemical induced mutations more than two times of the control and the concentration dependency was observed only in *Salmonella typhimurium* TA1537 without S9 at 2500 and 3000 ug/plate. Details of the tests were summarized below. In the two tests, MADAME caused the revertant colony increase of 2 times

as much as that of the control to *S.typhimurium* TA 1537 at 2,500 ug/plate without S9. But the concentration dependency was not clear.
Also the revertant colony increasing tendency was observed for *S.typhimurium* TA98 at 2500 ug/plate and 5000 ug/plate without S9.
The key results are summarized below.

[Results of reverse mutation of MADAME on bacteria]

Result, cont. : (without S9)

Items Test substance concentration (ug/plate)		Numbers of revertant colonies per plate [Mean ± S.D] TA 98	TA 1537
0	(1st)	17 18 24 [20 ± 4]	7 7 6 [7 ± 1]
	(2nd)	21 32 26 [26 ± 6]	6 7 5 [6 ± 1]
1250	(1st)	19 17 24 [20 ± 4]	7 6 8 [7 ± 1]
	(2nd)	26 15 27 [23 ± 7]	7 5 11 [8 ± 3]
2500	(1st)	30 44 30 [35 ± 8]	11 15 18 [15 ± 4]
	(2nd)	38 38 42 [39 ± 2]	18 14 13 [15 ± 3]
5000	(1st)	19* 46* 37* [34 ± 14]	4* 3* 6* [4 ± 2]
	(2nd)	33* 54* 27* [38 ± 14]	1* 4* 2* [2 ± 2]
Positive Control	(1st)	382 384 402 a) [389 ± 11]	1014 794 1030 b) [946 ± 132]
	(2nd)	413 432 372 b) [406 ± 31]	946 982 964 b) [964 ± 18]

*Toxic effect was observed.
a) AF-2 0.1 ug/plate
b) 9-AA: 9-Aminoacridine, 80 ug/plate

Result, cont. (Activation method: +S9)

Items Test substance concentration (ug/plate)		Numbers of revertant colonies per plate. [Mean ± S.D] TA 98	TA 1537
0	(1st)	25 41 40 [35 ± 9]	9 16 10 [12 ± 4]
	(2nd)	30 44 36 [37 ± 7]	19 21 18 [19 ± 2]

625 (1st)	39 35 33 [36 ± 3]	13 15 13 [14 ± 1]
(2nd)	39 27 37 [35 ± 5]	14 24 20 [19 ± 5]
1250 (1st)	35 42 48 [42 ± 7]	14 17 13 [15 ± 2]
(2nd)	25 44 34 [34 ± 10]	18 16 14 [16 ± 2]
2500 (1st)	37 32 41 [37 ± 5]	18 20 15 [18 ± 3]
(2nd)	34 46 40 [40 ± 6]	16 16 19 [17 ± 2]
5000 (1st)	52 54 37 [48 ± 9]	20 17 14 [17 ± 3]
(2nd)	38 58 32 [43 ± 14]	24 27 29 [27 ± 3]
Positive Control (1st)	301 258 265 [275 ± 23]	*85 80 103* [89 ± 12]
(2nd)	351 375 390* [372 ± 20]	100 88 82* [90 ± 9]

* +S9 mix. : 2-Aminoanthracene

Then, to confirm the concentration dependent increase of the revertant colony at between 2500 to 5000 ug/plate, the confirmation test was conducted for *S. typhimurium* TA 1537 and TA 98 by the direct method without S9.

Result, cont.

Toxic effect was observed at 3500 ug/plate and more to TA 98 and TA 1537 without S9 mix. As to TA 1537, the revertant colony increase was observed by morethan two times of the control at 2500 and 3000 ug/plate. Also the concentration dependency was observed. As to TA 98, although the revertant colony increase was observed at 2500 and 3000 ug/plate, it was less than two times as much as that of the control. The results of TA 1537 satisfied the following 3 conditions to be positive in the reverse mutation.

1) The revertant colony increase should be more than two times of the control.
2) The revertant colony increase should increase proportionally to the concentration of the test substance.
(The concentration dependency)
3) The same revertant colony increase should be observed repeatedly by more than two tests.
4) Then this chemical is considered to be positive in this reverse mutation test. The number of the induced revertant colonies/mg was calculated as 3.6/mg. The key results of the confirmation tests are shown below.

The results of the confirmation test are shown below.
(without S9)

Items	Numbers of revertant colonies
Test substance concentration	per plate [Means ± S.D] TA 98 TA 1537

		ug/plate	
		0	26 23 25 [25 ± 2] 5 4 5 [5 ± 1]
		1000	25 23 22 [23 ± 2] 8 8 5 [7 ± 2]
		1500	22 23 33 [26 ± 6] 9 11 7 [9 ± 2]
		2000	33 36 30 [33 ± 3] 8 7 9 [8 ± 1]
		2500	52 42 39 [44 ± 7] 12 11 16 [13 ± 3]
		3000	36 47 42 [42 ± 6] 13 11 21 [15 ± 5]
		3500	28* 29* 46* [34 ± 10] 7* 9* 6* [7 ± 2]
Result, cont.		4000	17* 22* 16* [18 ± 3] 5* 4* 3* [4 ± 1]
		4500	15* 7* 10* [11 ± 4] 3* 3* 4* [3 ± 1]
		5000	10* 15* 17* [14 ± 4] 3* 8* 4* [5 ± 3]
		Positive control	343 393 358 a) [365 ± 26] 933 962 905 b) [933 ± 29]

* Toxic effect was observed.
a) AF-2; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, 0.1 ug/plate
b) 9-AA; 9-Aminoacridine, 80 ug/plate

Source : MHW: Japan, 1998

Test condition : Procedures: Pre-incubation method
Solvent: Distilled water
Positive control:
-S9 mix.: For TA100, TA98, WP2 uvrA;
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide
For TA-1535: Sodium azide
For TA-1537: 9-Aminoacridine
+S9 mix.: 2-Aminoanthracene (all strains)
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plates/test : 3
Number of replicates: 2
By the preliminary test to decide the highest concentration, toxicity was observed at 5000 ug/ plate in the direct method without S9 mix for TA 98 and TA 1537. Then the highest concentration was set at 5000 ug/plate for all tests.
2 trial tests were done for all cells and a confirmation test was conducted for TA 98 and TA 1537 which showed positive results in the trial tests.

Test substance : The compositions of the test substance manufactured by Sanyo Kasei Co. Japan, were as follows: 99.9% MADAME, Impurities: Hydroquinone

monomethyl ether (as polymerization inhibitor) 2000 ppm, dimethyl amino ethanol less than 0.1%,methylmethacrylate less than 0.02%.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
10.01.2002 (33)

Type : Chromosomal aberration test
System of testing : Type of cell used: Chinese hamster lung (CHL/IU) cells
Concentration : [Continuous treatment]
20, 39, 78, 156, 313, and 625 ug/mL.
[Short-term treatment]
200, 400, 600, 800, 1400, and 1600 ug/mL.
Cycotoxic conc. : [Continuous treatment, 24 hrs]
625 ug/mL
[Continuous treatment, 48 hrs]
313 ug/mL
[6 hrs short-term treatment without S9 mix.]
800 ug/mL
[6 hrs short-term treatment with S9 mix.]
1600 ug
Metabolic activation : with and without
Result : Positive
Method : Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year : 1998
GLP : Yes
Test substance : other TS: 99.9% 2-(dimethyl amino)ethyl methacrylate, Sanyo -Kasei Co.
Result This chemical was positive in this test inducing chromosomal aberrations shown below.
By the 24 hrs and 48 hrs continuous treatment without S9, structural chromosomal aberrations (including gap) were induced at 625 ug/mL with 88.5% and 76.5% respectively. The numbers of cells with aberration except gap were 86.5% and 74.0% respectively. The cytotoxicity were observed at 625 ug/mL and 313 ug/mL respectively.
Polyploidy was not induced under these conditions.
By 6 h short-term treatment without S9, concentration-depending structural chromosomal aberrations (including gap) were induced at 200 ug/mL, 400 mg/mL and 600 ug/mL with 6.5%, 49.5% and 87.5%. The numbers of cells with aberration except gap were 6.5%, 46.0% and 86.0% respectively.
By 6 h short-term treatment with S9, concentration-depending structural chromosomal aberrations (including gap) were induced at 800 ug/mL, 1400 mg/mL and 1600 ug/mL with 13.5%, 99.5% and 100%. The numbers of cells with aberration except gap were 13.0%, 99.5% and 100.0% respectively.
Polyploidy was not induced under these conditions. At more than 800mg/mL on 6 h short-term treatment without S9 mix and at more than 1600 ug/mL with S9 mix, cytotoxicity was observed and the metaphase figures were not observable. As the results, MADAME is considered to induce chromosomal aberrations. However, the aberrations observed were mainly chromatid break and chromatid exchange. The data of these tests were summarized in the tables shown below.

Result, cont. : [Cell growth inhibition test results]

Cell growth inhibition test of CHL cells
continuously treated with 2-(dimethylamino) ethyl methacrylate
without S9 mix.

Concentration	Average cell growth rate (%)	
ug/mL	24-hour treatment	48-hour treatment
0 (Solvent)	100	100
78	66.0	62.5

156	61.5	50.0
313	58.0	39.0
625	26.5	20.5
1250	12.0	3.5
2500	10.0	3.0
5000	8.0	2.5

2 cell growth inhibition tests of CHL cells short-term treatment with 2-(dimethylamino) ethyl methacrylate with and without S9 mix.

Concentration ug/mL	Average cell growth rate (%) without S9	with S9
0 (Solvent)	100	100
600	56.5	81.0
800	41.5	70.5
1000	28.0	70.5
1200	18.0	70.5
1400	16.5	57.5
1600	11.5	43.5
1800	17.5	33.0

To decide the doses of chromosomal aberrasion test, a preliminary cell growth inhibition test was conducted. The cell growth ratios were determined for each doses. The cell growth ratio of the solvent (control) was defined as 100% and the cell growth ratios of each doses were determined as the % to the control group. In the case of continuous treatment, over 50 % growth inhibition was observed at 625 ug/mL and greater concentrations for 24 hours treatment. Therefore the cytotoxic concentration would be between 313 and 625 ug/mL. As for 48 hrs treatment, 50 % cell growth inhibition was observed at 156 ug/mL and more than 50 % growth inhibition was obesrved at 313 ug/mL or greater concentration for 48 hours treatment. In the case of short treatment, over 50% cell growth inhibition was observed at 800 ug/mL or greater concentrations without S9 and 1600 ug/mL or greater concentrations with S9. Then the cytotoxic concentration would be between 600 and 800 ug/mL without S9 and would be between 1400 and 1600 ug/mL. with S9.

Result, cont.

[Chromosome analysis of Chinese hamster cells (CHL) continuously treated with MADAME without S9 mix.]

Table 1-1. Chromosome analysis of Chinese hamster cells (CHL) continuously treated MADAME without S9 mix.

Time of exposure: 24 hours.
No. of cells analysed: 200 cells
Solvent: Distilled water
- g %: total no. of cells with aberration except gap (%)
+ g %: total no. of cells with aberrations
gap: gap ctd: chromatid break cte: chromatid exchange
csb: chromosome break
cse: chromosome exchange (dicentric and ring) oth: others
tot: total
MNNG: N-methyl-N'-nitro-N-nitrosoguanidine

Concentration of MADAME (ug/mL)	No. of structural aberrations						No. of cells with aberrations	
	gap	ctd	cte	csb	cse	ort	tot	-g (%)	+g (%)

Solvent	0	0	0	0	1	0	1	1 (0.5)	1 (0.5)
20	3	0	0	0	0	0	3	0 (0)	3 (1.5)
39	0	0	1	0	1	0	2	2 (1.0)	2 (1.0)
78	0	1	1	0	0	0	2	1 (0.5)	1 (0.5)
156	0	0	0	0	1	0	1	1 (0.5)	1 (0.5)
313	0	1	0	1	2	0	4	4 (2.0)	4 (2.0)
625	22	119	131	42	0	0	314	173 (86.5)	177 (88.5)*
(MNNG)									
2.5	11	32	185	7	0	0	235	188 (94.0)	189 (94.5)*

* Significantly different from solvent group data at P<0.01
by Fisher's exact test.

Table 1-2. Chromosome analysis of Chinese hamster cells (CHL) continuously treated with MADAME without S9 mix.

Time of exposure: 48 hours
No. of cells analysed: 200 cells
Solvent: Distilled water
- g %: total no. of cells with aberration except gap (%)
+ g %: total no. of cells with aberrations
gap: gap ctd: chromatid break cte: chromatid exchange
csb: chromosome break
cse: chromosome exchange (dicentric and ring) oth: others
tot: total.
MNNG: N-methyl-N'-nitro-N-nitrosoguanidine

Result, cont.

Concentration of MADAME (ug/mL)	No. of structural aberrations							No. of cells with aberrations	
	gap	ctd	cte	csb	cse	ort	tot	-g (%)	+g (%)
solvent	1	0	1	0	0	0	2	1 (0.5)	2 (1.0)
20	0	0	0	0	1	0	1	1 (0.5)	1 (0.5)
39	0	0	0	0	0	0	1	0 (0)	1 (0.5)
78	2	0	0	1	1	0	4	2 (1.0)	4 (2.0)
156	0	0	0	0	0	0	0	0 (0)	0 (0)
313	1	0	0	0	2	0	3	2 (1.0)	3 (1.5)
625	21	61	123	46	0	0	251	148 (74.0)	153 (76.5)*
(MNNG)									
2.5	11	39	136	25	17	0	228	159 (79.5)	159 (79.5)*

* Significantly different from solvent group data at P<0.01
by Fisher's exact test.

[Chromosome analysis of Chinese hamster cells (CHL) treated with MADAME with and without S9 mix.]

Table 2-1 Chromosome analysis of Chinese hamster cells (CHL) short-term treatment with MADAME without S9 mix.

Time of exposure: 6-(18) hours
No. of cells analysed: 200 cells
Note: At 800,1400 and 1600 ug/mL, no. of cells can't be counted and analyzed due to toxicity.
Solvent: Distilled water
BP: benzo[a]pyrene
- g %: total no. of cells with aberration except gap (%)
+ g %: total no. of cells with aberrations
gap: gap ctd: chromatid break cte: chromatid exchange

csb: chromosome break cse: chromosome exchange (dicentric and ring)
oth: others tot: total

Result, cont.

Concentration of MADAME (ug/mL)	No. of structural aberrations							No. of cells with aberrations	
	gap	ctd	cte	csb	cse	ort	tot	-g (%)	+g (%)
Solvent	0	0	0	0	1	0	1	1 (0.5)	1 (0.5)
200	1	1	6	0	6	0	14	13 (6.5)	13 (6.5)*
400	18	23	86	6	0	0	133	92 (46)	99 (49.5)*
600	28	115	141	21	0	0	305	172 (86.0)	175 (87.5)*
800	Toxicity								
1400	Toxicity								
1600	Toxicity								
BP									
10	1	1	2	0	0	0	4	3 (1.5)	4 (2.0)

* Significantly different from solvent group data at P<0.01 by Fisher's exact test.

Table 2-2 Chromosome analysis of Chinese hamster cells (CHL) short-term treatment with MADAME with S9 mix.

Time of exposure: 6-(18) hours
No. of cells analysed: 200 cells, At 1600 ug/mL, 84 cells were analyzed.
Solvent: Distilled water
BP: benzo[a]pyrene
- g %: total no. of cells with aberration except gap (%)
+ g %: total no. of cells with aberrations
gap: gap ctd: chromatid break cte: chromatid exchange
csb: chromosome break
cse: chromosome exchange (dicentric and ring) oth: others
tot : total

Concentration of MADAME (ug/mL)	No. of structural aberrations							No. of cells with aberrations	
	gap	ctd	cte	csb	cse	ort	tot	-g (%)	+g (%)
Solvent	0	0	1	0	0	0	1	1 (0.5)	1 (0.5)
200	0	0	0	0	2	0	2	2 (1.0)	2 (1.0)
400	0	0	0	0	0	0	0	0 (0)	0 (0)
600	1	1	3	0	2	0	7	6 (3.0)	7 (3.5)
800	2	2	24	0	2	0	30	26 (13.0)	27 (13.5)*
1400	13	146	194	45	0	0	398	199 (99.5)	199 (99.5)*
1600	6	60	81	21	0	0	168	84 (100)	84 (100)*
BP									
10	9	11	112	1	2	0	138	116 (58.0)	117 (58.5)*

* Significantly different from solvent group data at P<0.01 by fisher's exact test.

Source : MHW: Japan, 1998

Test condition : Solvent: Distilled water
Positive control: -S9 mix, N-Methyl-N'-nitro-N-nitrosoguanidine
+S9 mix, Benzo[a]pyrene
Doses: -S9 mix. (24 and 48-hr continuous treatment) : 0, 20, 39, 78 156, 313, 625 ug/mL
-S9 mix. (6-hr short-term treatment) : 0, 200, 400, 600, 800, 1400, 1600 ug/mL

+S9 mix. (6-hr short-term treatment): 0, 200, 400, 600,800, 1400, 1600 ug/mL
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone

Plate/test: 2

By the preliminary cytostatic test to know the cytotoxicity doses, following cytotoxicity doses were revealed.
[Continuous treatment, 24 hrs] 625 ug/mL
[Continuous treatment, 48 hrs] 313 ug/mL
[6 hrs short-term treatment without S9 mix.] 800 ug/mL
[6 hrs short-term treatment with S9 mix.] 1600 ug/mL
Based on these data, above shown doses were decided for these tests.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
10.01.2002 (33)
Type : Cytogenetic assay
System of testing : Human lymphocytes
Concentration : 0, 66.39, 88.52, 118.0, 157.4, 209.8, 279.8, 373, 497.4, 663.2, 884.3, 1179, 1572 ug/Ml
Cycotoxic conc. :
Metabolic activation : with and without
Result : positive.
Method : other
Year : 1991
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Remark

The cells sampled at 20 hours after the start of treatment, were analysed for the chromosomal aberrations. At the higher two concentrations, namely 1179 ug/mL without S9 and 1572 ug/mL with S9, this chemical induced the aberrations which were significantly different from those observed in the concurrent solvent controls. No exchange-type aberrations were observed, but only the deletion-type aberrations were seen. The numbers of cells with aberration including gap (average of two tests) at 1179 ug/mL without S9 and 1572 ug/mL with S9 were 19.5% and 12.5% respectively.The numbers of cells with aberration exccluding gap (average of two tests) at 1179 ug/mL without S9 and 1572 ug/mL with S9 were 11.0% and 7.5% respectively. No marked mitomic inhibition was evident in any of the doses analysed in this study.
The mitomic index at 1179ug/mL without S9 and 1572 ug/mL with S9 (average of two tests) were 2.3% and 6.2 % respectively. It is concluded that MADAME may induce the chromosomal aberrations in the human peripheral blood lymphocytes.

ABERRATIONS OBSERVED
[Without S9]

Items	Solvent			884.3 ug/mL			1179 ug/mL			50 ug/mL (MMS)		
	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B
Culture												
Cells scored:	100	100	200	100	100	200	100	100	200	25	25	50
Gaps	3	3	6	3	6	9	11	6	17	32	5	
Chr. del.	0	1	1	1	0	1	1	3	4	5	2	7
Chr. exch	0	0	0	0	0	0	0	0	0	0	0	0
Ctd. del.	0	0	0	8	5	13	11	7	18	4	5	9
Ctd. exch	0	0	0	0	0	0	0	0	0	3	4	7
Other.	0	0	0	0	0	0	0	0	0	0	0	0

Summary of aberrations observed
MITOTIC INDEX (%)

TREATMENT (UG/ML)	20 HOURS			
	- S 9		+ S 9	
	A	B	A	B
SOLVENT	5.6	6.0	6.3	6.8
66.39	NM	NM	NM	NM
88.52	NM	NM	NM	NM
118.0	NM	NM	NM	NM
157.4	NM	NM	NM	NM
209.8	NM	NM	NM	NM
279.8	NM	NM	NM	NM
373.0	6.2	4.8	NM	NM
497.4	6.0	4.3	7.2	4.6
663.2	4.8	4.9	6.0	5.2
884.3	4.3	3.9	6.8	6.5
1179.0	2.3	2.2	6.4	5.3
1572.0	0	0	6.2	6.2

NM: NOT MADE

Remark, cont. : Total

incl gaps	3	4	7	12	11	23	23	16	39	15	13	28
(%)	(3.5)			(11.5)			(19.5)			(14.0)		
excl gaps	0	1	1	9	5	14	12	10	22	12	11	23
(%)	(0.5)			(7.0)			(11.0)			(11.5)		

[With S9]

Items	Solvent			1179 ug/mL			1572 ug/mL			25 ug/mL (CPA)		
	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B
Culture												
Cells scored:	100	100	200	100	100	200	100	100	200	25	25	50
Gaps	2	3	5	4	3	7	7	3	10	5	3	8
Chr. del.	0	1	1	2	0	2	2	2	4	1	1	2
Chr. exch	0	0	0	0	1	1	0	0	0	0	0	0
Ctd. del.	1	0	1	1	3	4	5	6	11	14	10	24
Ctd exch	0	0	0	0	0	0	0	0	0	1	1	2
Other	0	0	0	0	0	0	0	0	0	0	0	0
Total												
incl gaps	3	4	7	7	7	14	14	11	25	21	15	36
(%)	(3.5)			(7.0)			(12.5)			(18.0)		
excl gaps.	1	1	2	3	4	7	7	8	15	16	12	28
(%)	(1.0)			(3.5)			(7.5)			(14.0)		

Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (4)

Type : HGPRT assay
System of testing : V79 Chinese Hamster Cells

Concentration	:	with S9 mix : 62.5 - 125 - 250 - 500 - 1000 - 1500 - 2000 ug/mL ; without S9 mix : 31.25 - 62.5 - 125 - 250 - 500 ug/mL
Cycotoxic conc.	:	> 1000 ug/mL
Metabolic activation	:	with and without
Result	:	Negative
Method	:	OECD Guideline 476 "Genetic Toxicology: *In vitro* Mammalian Cell Gene Mutation Tests"
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Although round and refringent cells were observed at 250 ug/mL, the mutation frequency in the cells from duplicate cultures treated with MADAME was considered as similar to that of the negative and solvent controls, with and without S9: i.e. no significant increase (3 fold increase over the controls) was observed. MADAMe did not show mutagenic activity in this HPRT gene mutation aasay in V 79 Chinese hamster cells.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test condition	:	Metabolic activation: S9 mix microsomal rat liver portion and cofactor. By the preliminary cytotoxicity test, the cytotoxicity (decrease in the cloning efficiency and/or dead cells) was shown at the concentrations of equal or greater than 1000 ug/mL, both with or without S9 mix. At 250 ug/mL or higher, round and refringent cells were observed.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
10.01.2002	(5)	

Type	:	*Salmonella typhimurium* reverse mutation assay
System of testing	:	Strains TA1535, TA 1537, TA 1538, TA 98, TA 100
Concentration	:	100 - 500 - 1000 - 2500 and 5000 ug/plate
Cycotoxic conc.	:	slight toxicity at 5000 ug/plate for TA 100
Metabolic activation	:	with and without
Result	:	Negative
Method	:	OECD Guideline 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year	:	1991
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The test substance, MADAME, did not induce a significant increase in the revertant number with or without S9 mix in any of 5 strains. The negative and solvent control results were equivalent to those usually obtained in this Laboratory. The number of revertants induced by the positive control was higher than the spontaneous one, which demonstrateted the sensitivity of this test and the efficacy of the S9 mix throughout this study.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test condition	:	Metabolic activation : S9 mix microsomal rat liver portion and cofactor -S9 mix.: Sodium azide(NaN3) for TA 1535 and TA 100 9-amino-acridine (9AA) for TA 1537 2-nitrofluorene (2NF) for TA 1538 and TA 98 +S9 mix.: 2-anthramine (2AM) for all strains
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
09.01.2002		(3)

5.6 Genetic toxicity 'in vivo'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	gavage
Exposure period	:	one dose
Doses	:	1000 mg/kg (maximum tolerated dose)
Result	:	negative
Method	:	OECD Guideline 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1989
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	In comparison with the corresponding negative controls there was no substantial enhancement in the frequency of the detected micronuclei at any preparation interval after application of the test article. The mean values of micronuclei observed after treatment with MADAME were in the same range compared to the negative control groups. In the positive control group a distinct increase of induced micronuclei frequency was observed.In conclusion, the test article did not induce micronuclei as determined by the micronucleus test in the bone marrow cells of the mouse.

[Summary of the test results]

Sampling time: 24 hrs

Group	Dose mg/kg bw	PCEs with Micronuclei (%)	Micronuclei in 1000 PCE (Range)	PCE/NCE (mean)
Solvent	0	0.06	0 – 2	1000 / 554
Test article	1000	0.03	0 – 2	1000 / 653
CPA	40	0.75	1 – 13	1000 / 742

Sampling time: 48 hrs

Group	Dose mg/kg bw	PCEs with Micronuclei (%)	Micronuclei in 1000 PCE (Range)	PCE/NCE (mean)
Solvent	0	0.04	0 – 2	1000 / 680
Test article	1000	0.04	0 – 1	1000 / 744

Remark, cont. : Sampling time: 72 hrs

Group	Dose mg/kg bw	PCEs with Micronuclei (%)	Micronuclei in 1000 PCE (Range)	PCE/NCE (mean)
Solvent	0	0.06	0 – 4	1000 / 594
Test article	1000	0.09	0 – 2	1000 / 506

CPA : cyclophosphamide
PCE : polychromatic erythrocytes
NCE : normochromatic erythrocytes

Source	:	Roehm, EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test condition	:	Group: 5 males and 5 females Negative control: distilled water Positive control: Cyclophosphamid in physiological serum (NaCl)

Dose: 40 mg/kg
Bone marrow preparation: 24, 48 and 72 hrs after application.
Analysis : 1000 PCE (Polychromatic Erythrocytes) per animal
By a preliminary test, 1000 mg/kg b.w. was estimated to be the maximum tolerated dose. The animals expressed toxic reactions. After treatment with the test article the ratio between PCEs and NCEs was not affected as compared to the corresponding negative controls, thus indicating no cytoyoxic effects.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
10.01.2002 (52)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : Swiss OF1/ICO:OF1 IFFA-CREDO
Route of admin. : i.p.
Exposure period : 2 administrations separated by 24 hrs
Doses : 200 mg/kg
Result : negative
Method : OECD Guideline 474 "Genetic Toxicology: Micronucleus Test"
Year : 1993
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Remark : Group: 5 males and 5 females
2 administrations by 24 hrs via intraperitoneal route. 200 mg/kg MADAME in 10 mL isotonic solution 0.9% NaCl was administratedd to mouse.
Positive control: Cyclophosphamide
Dose: 25 mg/kg (2 ip injectons)
Bone marrow preparation 24 h and 48 h after the 2nd administration.
Analysis : the presence of micronuclei in 2000 polychromatic erythrocytes per mouse and the ratio of PCE/NCE.

Result : In all groups treated with MADAME, the mean values of micronucleated polychromatic erythrocytes were similar to those of their respective vehicle groups at each sampling time, and no statiscally significant differences were observed. The PE/NE ratio did not differ from that of the respective vehicle control group.
MADAME did not induce cytogenetic damage to the bone marrow cells of mice when treated twice separated by 24 hrs by intraperioneal route at 200 mg/kg in the micronucleus test.

[Summary of the test results]

Time of sacrifice: 24 hrs after the 2 nd administration

Group	doses	MPE/PE	PE/NE ratio
---------	(mg/kg)	Mean (SD)	Mean (SD)
vehicle	-----	2.0 (0.8)	0.7 (0.2)
Test substance	200	1.9 (1.1)	0.6 (0.2)
CPA	25	18.2 (3.8)#	0.4# (0.1)

Time of sacrifice: 48 hrs after the 2 nd administration

Group	doses	MPE/PE	PE/NE ratio
---------	(mg/kg)	Mean (SD)	Mean (SD)
vehicle	-----	1.9 (0.8)	0.9 (0.4)
Test substance	200	1.7 (1.0)	1.2 (0.6)

10 animals (5 males, 5 females) per group

: P < 0.001

Vehicle: physiological solution
CPA : cyclophosphamide
PE : polychromatic erythrocytes
NE : normochromatic erythrocytes
MPE/PE: micronucleated polychromatic erythrocytes/1000 Polychromatic erythrocytes.
(SD) : standard deviation.

Source : Atochem Paris la Defense, 1993
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2002 (7)

5.7 Carcinogenity

5.8 Toxicity to reproduction

Type : other
Species : rat
Sex : male/female
Strain : Crj: CD(SD)
Route of admin. : gavage
Exposure period : Males, 14 days before mating Females, from 14 days before mating to day 3 of lactation
Frequency of treatment : Once daily
Premating exposure period.
Male : 14 days
Female : 14 days
Duration of test : 41-52 days
Doses : 0(Vehicle), 40, 200, 1000 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Parental : = 200 mg/kg bw
Method : OECD combined repeated dose and reproductive/developmental toxicity screening test
Year : 1998
GLP : yes
Test substance : other TS: 99.9% purity, Sanyo-Kasei Co., Japan
Remark As the LD50 value of > 2000 mg/kg was known, a preliminary test to decide the highest dose level at 30, 100, 300 and 1000 mg/kg/day for 14 days was conducted. At 1000 mg/kg/day, decrease of body weight in males and suppression of body weight increase in females were observed. Then the highest dose level for the test was set at 1000 mg/kg/day.
Result : NOAELs = 1000 mg/kg/day for males
= 200 mg/kg/day for females
= 200 mg/kg/day for offsprings

The compound had no effects on reproductive parameteres such as the mating index, the fertility index, numbers of corpora lutea or implantations, the implantation index, the delivery index, the gestation index, gestation length or parturition. Three dams of the 1000mg/kg group, however, lost all their pups in the lactation period. As reported in 5.4 repeated dose toxicity, significant adverse effects were observed in animals of 1000 mg/kg/day group, especially in females. These adverse effects observed in females

were as follows:
* 3 females out of 12 died.
* By the observation, late onset of twitching, chronic convulsion, suppression of body weight gain and a decrease in food consumption in lactation period were observed.
* By the histopathological examination, the degeneration of nerve fibers in the brain and the spinal cord, and the hyperplasia of the mucosa in gastric tract,the edema and inflammatory cell infiltration in the forestomach, and the atrophy of thethymus were revealed.
Also the increases in the weight of the kidneyand the adrenals without histopathological changes were observed.

On examination of neonates, the 1000 mg/kg dosewas associated with a decreasein body weight and a low viability index.

There were no significant differences in number of offspring or live offspring, the sex ratio or the live birth index. No abnormalities ascribable to the compound were found for external features, clinical signs or necropsy findings for the offspring. The key data are summarized in the table shown below.

Result, cont. :

[Reproductive parameters]

Dose (mg/kg)	0	40	200	1000
Number of pairs examined	12	12	12	10
Numbers of pairs with successful mating	12	12	11	10
Mating index (%)	100.0	100.0	91.7	100.0
Number of pregnant females	12	12	11	9
Fertility index (%)	100.0	100.0	100.0	90.0
Pairing days until mating	2.5 ± 1.0	3.1 ± 1.0	3.9 ± 3.0	2.8 ± 1.0
Number of estrous stages without mating*	0.0	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0

Mating index (%) = (No. of pairs with successful mating /No. of pairs examined)x100
Fertility index (%) = (No. of pregnant animals / No. ofpairs with successful mating) x 100
* Values are expressed as Mean ± S.D.

[developmental parameters]

Dose (mg/kg)	0	40	200	1000
Number of females examined	12	12	11	8
Live birth	98.03 ±	100.00 ±	93.18 ±	89.06 ±

	index* (%)	4.52	0.00	22.61	12.64
	Numbers of live pups on day 0	14.3 ± 1.6	15.5 ± 1.2	13.1 ± 5.1	11.0 ± 3.7
	Nummbers of live pups on day 4*	14.0 ± 1.5	15.5 ± 1.2	14.0 ± 3.7	7.8 ± 4.2
	Body weight of pups (g)				
Result, cont.	On day 0				
	Male*	7.2 ± 0.4	6.6 ± 0.4	6.9 ± 0.7	6.4 ± 1.1**
	Female*	6.8 ± 0.6	6.3 ± 0.5	6.5 ± 0.7	6.0 ± 0.9**
	On day 4				
	Male*	11.1 ± 1.1	10.4 ± 0.9	10.8 ± 2.0	10.2 ± 2.5
	Female*	10.7 ± 1.3	9.8 ± 1.0	10.4 ± 2.0	9.8 ± 1.8

*: Value are expressed as Mean ± S.D.
**: Significantly different from control ; p<0.05.

Source : MHW: Japan, 1998
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
10.01.2002 (33)

5.9 Developmental toxicity/teratogenicity

5.10 Other relevant information

Type : Cytotoxicity
Remark : Result : Cell growth inhibition in Balb/c 3T3 Fibroblasts. ID50 > 100 umol/l (endpoints observed : inhibition of DNA synthesis, protein synthesis, total protein content, irriversible inhibition of cell metabolism.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (19)

Type : Metabolism
Remark : Result : The subtance was rapidly hydrolysed to methacrylic acid and N,N,-dimethylaminoethanol when incubated with simulated saliva or simulated intestinal fluid in vitro. 90 % degradation was observed in simulated saliva after 4 hours at 37°C, 86 % degradation after incubation with simulated intestinal fluid for 4 hours at 37°C. Degradation was below 8 % after incubation with simulated gastric fluid for 4 hours at 37°C.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (6)

Type : Metabolism
Remark : Small quantities of mathacrylates may readily be metabolized by

saponification into the alcohol and methacrylic acid. The latter may form acetyl-CoA derivatives, which then enters the normal lipid metabolism.

Source : Clayton/Patty
10.01.2002 (13)

Type : other
Remark : 1) Anesthetized dogs following intraveneous administration of 2.4, 4.7, 9.7, 18.9 mg/kg
* Increase the respiratory rate
* Decrease the heart rate
* Hypertension blood, Effect up to 30-40 mn

2) Effects on isolated rabbit heart following perfuse with solutions 1/1000, 1/10000, 1/100000 (v/v)
* Decrease in the heart rate, force of contraction and coronary flow

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (34)(35)

Type : other
Remark : Effects on smooth muscles were stu died on guineapig isolated ileum.
3 concentrations: 1/25000; 1/50000; 1/100000.
At 1/100000, Increase of contractility.
Atropin (0.1 mug/ml) dit not antagonise the effects.

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (34)

Type : other
Remark : Route of administration: i.v.
Species: Rat with sarcoms 45 or mammary carcinomas
Result: Decrease of neoplastic, dystrophic and necrotic changes of tumours.
No data on doses and duration of injections

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (29)

Type : other
Remark : Species: rabbit
Route of Administration: gavage
Result: Decrease of electrical and cerebral activity and clonico-tonic convulsions. Chronic studies in rats and rabbits with 0.1 x LD16 did not affect growth, blood parameters, electrolytic equilibrium, weight of organs and renal and hepatic functions.

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
18.05.1994 (36)

Type : other: Enzyme inhibition *in vitro*
Remark : Result : The substance did not inhibit cholinesterase activity of the isolated enzyme or in rat brain preparations *in vitro*.

Source : Atochem Paris la Defense
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7.1 End point summary

7.2 Hazard summary

7.3 Risk assessment