FOREWORD INTRODUCTION

Methacrylamide

CAS N°: 79-39-0

SIDS Initial Assessment Report

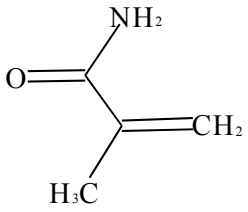
For

SIAM 15

Boston, October 22 – 25, 2002

1. Chemical Name:	Methacrylamide
2. CAS Number:	79-39-0
3. Sponsor Country:	Japan National SIDS Contact Point in Sponsor Country: Mr. Yasuhisa Kawamura Director Second Organisations Div. Ministry of Foreign Affairs 2-2-1 Kasumigaseki, Chiyoda-ku Tokyo
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Mr. Katsuhiko Inaba, Mitsui Chemicals, Inc. E-mail: katsuhiko.inaba@mitsui-chem.co.jp
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 15.
7. Review Process Prior to the SIAM:	The industry 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 ( )
8. Quality check process:	
9. Date of Submission:	
10. Date of last Update:	
11. Comments:	The industry contact point is Mr. Katsuhiko Inaba, Mitsui Chemicals, Inc.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-39-0
Chemical Name	Methacrylamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After i.v. administration of ^{14}C-methacrylamide (15% solution in water) , most of the radioactivity (86 % of the dose) was excreted with the urine within 24 hours in rabbits. Following 15 to 30 minute dermal exposure to male rabbits and male rats, 23-52% and 3.7-5.7% of the administered radioactivity, respectively, were excreted in urine after 24 hours. Phenobarbital induction increased the reaction rate about 2-fold suggesting a cytochrome P-450 dependent metabolism.

Acute oral toxicity of methacrylamide in rats is: LD_{50} = 1653-1938 mg/kg [OECD TG 401]. In one study, tremor was found at 1315 mg/kg and higher. Salivation, staggering gait, irritability, soiled perioral fur, sitting position and orange-yellow urine in cage trays were observed at 1512 mg/kg and higher. Histopathological changes were observed in the testes and epididymides in males at 1512 mg/kg and higher. Necrosis of neurocyte cell in cerebellum was observed at 1315 mg/kg and higher of both sexes. Degeneration of sciatic nerve fibers was observed in males at 1512 mg/kg and in females at 1739 mg/kg. In the other study, sedation, ataxia, mortality, ruffled fur, ventral/curved/or latero-abdominal body position, somnolence, emaciation, and lacrimation were observed. Methacrylamide was not to slightly irritating to skin in rabbits [OECD TG 404] and moderately irritating to eyes in rabbits [OECD TG 405]. There is no available information on skin sensitization.

In a 28 day repeated dose study in rats [OECD TG 407] by gavage at the dose levels of 0, 30, 100 and 300 mg/kg/day, body weight gain and food and water consumption were decreased in both sexes at 300 mg/kg/day. A decrease in body weight gain was also observed in females at 100 mg/kg/day. Some clinical and functional changes (decrease in muscle tone, ataxia and decrease in grip strength) were found at 300 mg/kg/day. Males at 100 mg/kg/day and higher and females at 30 mg/kg/day and higher showed a decrease in locomotor activity. These functional changes were observed continuously throughout the recovery period. Histopathological examination revealed a degeneration of the sciatic nerve fibers and axonal swelling in the cerebellar peduncle at 300 mg/kg/day of both sexes. At 300 mg/kg/day, a decrease in hematocrit, hemoglobin, MCH, urea nitrogen, creatinine, alpha1-globulin, alpha2-globulin and ALP, and an increase in albumin and triglyceride were noted. At 100 mg/kg/day, a decrease in hemoglobin and MCH were noted. At the end of the recovery period, an increase in absolute and relative testis weights was found. NOAELs were considered to be 30 mg/kg/day for males and less than 30 mg/kg/day for females.

A 12 month repeated dose toxicity study in male rats and male mice given methacrylamide in drinking water (200, 400, 800 and 1200 ppm corresponding to ca. 4.6, 9.1, 19.5 and 31.6 mg/kg for rats, and ca. 24.3, 49.6, 120 and 220.6 mg/kg/day for mice) was also conducted. For rats, at 800 ppm (ca. 19.5 mg/kg/day) and higher, reduction in the rotarod performance, distension of the urinary bladder, shrinkage and loss of myelinated fibers of sciatic nerve, and atrophy of gastrocnemius muscle were observed. Symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait were noted in the highest dose group. Serum total cholesterol and phospholipid content were increased significantly at the highest dose. In mice, reduction in the rotarod performance, symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait, atrophy of gastrocnemius muscle, distension of the urinary bladder and decrease in body weight gain were seen at 800 ppm (ca. 120mg/kg/day) and higher. At 400 ppm (ca.49.6 mg/kg/day) and higher, paralysis of hindlimb, shrinkage and loss of myelinated fibers

of sciatic nerve were observed. The NOAELs for the 12 month repeated dose study were considered to be ca. 9.1 mg/kg/day (400ppm) for rats and ca. 24.3 mg/kg/day (200ppm) for mice.

The lowest NOAEL for repeated dose toxicity was considered to be ca. 9.1 mg/kg/day obtained from the 12 month repeated dose toxicity study based on clinical signs, rotarod performance and histopathological changes of the nervous system.

In a preliminary Reproduction Toxicity Screening Test by oral administration in Rats [OECD TG 421], this substance was administered at 0, 12.5, 50 and 200 mg/kg/day. A decrease in the maternal copulation rate, delayed parturition and abnormal nursing were found at 200 mg/kg/day. Furthermore low body weights and decreased viability of the pups were also found at 200 mg/kg/day. 50 mg/kg/day was considered to be the NOAEL for reproductive and developmental toxicity in this study. However, the changes observed in pups might be related to severe maternal toxicity.

A two-generation reproductive toxicity study with mice given methacrylamide in drinking water was conducted according to the modified RACB (the National Toxicology Program's Reproductive Assessment by Continuous Breeding Protocol). In this study, F_0 and F_1 animals were dosed for approximately 100 days (24 – 240 ppm corresponding to 4.5 – 49 mg/kg/day) and 74 days (24-240 ppm corresponding to 6.8 - 71.3 mg/kg/day), respectively. No maternal nor reproductive toxicity was observed in both generations. The NOAELs of methacrylamide are considered to be 49 mg/kg/day for F_0 and 71.3mg/kg/day for F_1.

Based on the results of the two studies, the lowest NOAEL of methacrylamide for reproductive toxicity was considered to be 49 mg/kg/day.

In a developmental toxicity study, methacryamide was administered to pregnant mice from gestation day 6 to gestation day 17 at the dose levels of 60, 120 and 180 mg/kg/day. Increased postimplantation death per litter at 180 mg/kg/day and reduction of fetal body weight at 120 mg/kg/day and higher were found. External anomalies in offspring were not observed. 60 mg/kg/day was considered to be the NOAEL for developmental toxicity in this study.

In the two-generation reproductive toxicity study (4.5 - 49 mg/kg/day for F_0 and 6.8 - 71.3 mg/kg/day for F_1), the hindlimb grip strength was reduced in three- week- old male and female F_1 offspring in all dose groups. However, this effect became insignificant when animals grew older at 6.8 and 23.8 mg/kg/day.

Based on these results, the NOAEL of methacrylamide for developmental toxicity was considered to be less than 6.8 mg/kg/day.

As mentioned above, methacrylamide has neurotoxic effects.

Methacrylamide was not mutagenic in bacteria up to 5,000 ug/plate [OECD TG 471] and not clastogenic in CHL/IU cells up to 900 ug/mL (10 mM) [OECD TG 473]. It also gave a negative response in a dominant lethal assay conducted as a part of a modified reproductive assessment. Males after treatment of methacrylamide (4.5 – 49 mg/kg/day) for approximately 100 days were cohabited with untreated females. No dominant lethal effects were observed. However, with reference to the structural similarity with acrylamide, uncertainty remains with regards to mutagenicity.

The available data are insufficient to judge the carcinogenicity potential of this chemical.

Environment

Methacrylamide is soluble in water (>=100g/L at 25°C). Its vapor pressure is estimated to be low (1.3×10^{-4} hPa at 25 °C). This substance is readily biodegradable and has a low bioaccumulation potential based of its log Pow (-0.15). Methacrylamide will react in the atmosphere with photochemically-produced hydroxyl radicals with a half life of 0.5 day. The fugacity model (Mackay level III) suggests that if released to the environment, the majority of this substance would distribute into water and soil.

In acute toxicity studies, the EbC_{50} and ErC_{50} for green algae [OECD TG 201] and the EC_{50} for Daphnia [OECD TG 202] were greater than 1000 mg/L. LC_{50} for fish were greater than 100 mg/L [OECD TG 203] and 2730 mg/L [other method], respectively. In a chronic toxicity study with Daphnia [OECD TG 211], the NOEC was greater than 100 mg/L. As for chronic toxicity in green algae, the NOEbC and NOErC were 556 mg/L and greater than 1000 mg/L, respectively.

Exposure

The production volume of the substance in 2001 is estimated at ca. 3500 tonnes/year in Japan and the production capacity in the EU is ca. 5000 tonnes/year.

It is mainly used as a raw material for polymerized compounds such as emulsions (liquid that includes many minute floating particles) or latex, whose applications are textile-finishing agent, paper finishing agent, coating agent, condensing agent, etc. The residual monomer content in polymers is ca. 0.5% or less. Typical residual monomer contents are 0.001% to 0.01%. Migration of residual unpolymerized methacrylamide from polymer articles is very low, as typified by migration into food simulants under EU food regulations for plastic materials (Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs). The Specific Migration Limit (SML) is below 0.02 mg/kg. Hence exposure of this substance to consumers is very low.

Because of its use limited to industries and its low vapor pressure, release of this substance into air and soil is very low. At the production sites waste and residues of the production process are incinerated. It is considered that release to water through sewage treatment system is the most important exposure route to the environment. The concentrations of methacrylamide in the influent of the sewage treatment plant was 2100 mg/L. In the effluent and the river water downstream from the outfall of the industrial site the concentration was below 1 mg/L. Measurement data at ca. 400 meters down stream from the outfall of the industrial site show concentrations of below 0.1 mg/L – 0.3 mg/L

Based on usage and properties of methacrylamide, only occupational exposure via inhalation and dermal routes is considered to be possible, and consumer exposure is not expected.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

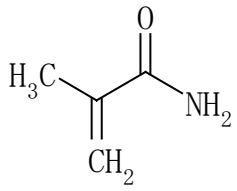
This chemical is currently of low priority for further work because of its low environmental hazard potential and because it is anticipated based on data presented by the Sponsor country that the exposure to humans is low. However, the substance has properties indicating hazards for human health (developmental toxicity and neurotoxicity) and uncertainty regarding mutagenicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. It is noted that a micronucleus assay will be conducted.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 79-39-0
IUPAC Name: 2-Methyl-2-propenamide
Molecular Formula: C_4H_7NO
Structural Formula:



Synonyms: 2-Methacrylamide
2-Methyl-2-propenamide
2-Methylacrylamide
2-Methylpropenamide
2-Propenamide, 2-methyl- (9CI)
α-Methyl acrylic amide
Methacrylamide(8CI)
Methacrylic acid amide
Methacrylic amide
Methylacrylamide
Prop-2-enamide, 2-methyl- (PICCS)

1.2 Purity/Impurities/Additives

Purity: >= 99.0 % weight/weight.

Impurities: Sodium methacrylate

Ammonium sSulfate

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

ITEMS	PROTOCOL	RESULTS
Melting Point	Other: unknown	111.3 °C
Boiling Point	JIS K 2233-1984	225 °C (at 1,013 hPa)
Density	JIS K 7112-1980	1.138 g/cm^3 (at 25°C)
Vapor Pressure	OECD TG 104	1.3 x 10^{-4} hPa (at 25°C)
Partition Coefficient (Log Pow)	OECD TG 107	-0.15 (at 25°C)
Water Solubility	OECD TG 105	>= 100.0 g/L (at 25°C)
pKa	OECD TG 112	Dissociation not being occurred
Stability in water	OECD TG 111	Stable ($t_{1/2}$ > 5 days at 50°C at pH 4,7 and 9)
Minimum explosive Concentration	Other	55 mg/L

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

- The production volume of the substance in 2001 is estimated at ca. 3500 tonnes/year in Japan and the production capacity in the EU is estimated to be ca. 5000 tonnes/year.
- Methacrylamide is exported from the sponsor country to many regions excluding Africa (out of South Africa) and Oceania.
- Methacrylamide is produced in a semi-closed system, hence emissions during production are estimated to be low.
- The substance is mainly used as a monomer for the synthesis of polymers.
- Therefore, the exposure of the substance is limited to industrial uses.
- Due to the application of the substance (mostly for industrial use), consumer use is not relevant.
- During the production of the substance and the polymerization process in Japan, workers may be exposed to this substance only at the production sites and industrial sites, since this substance is limited to industrial use.
- Residual monomer content of polymer is ca. 0.5% or less.
- Migration of monomer to food simulant from polymer is very low.
- The aquatic release of the substance from the production sites is low and monomers would not be persistent in the environment because of its ready biodegradability and low bioaccumulation potential. Thus, exposure to environmental organisms is considered to be low.

2.2 Environmental Exposure and Fate

A generic fugacity model (Mackay level III) suggests that if released to the environment, the majority of the substance would distribute into water and soil as shown in Table 2 (Mitsui Chemicals, 2002).

Based on its physical properties (low vapor pressure) and uses limited to industries, this substance is considered to be released mainly to water. A fugacity model (Table 1) shows that close to 100 % of this substance released to water would remain in water.

Methacrylamide, if released to the air compartment, will react with photochemically-produced hydroxyl radical or ozone with a half life of 0.5 day or 1.0 day, respectively. (SRC AOP V.1.90).(Mitsui Chemicals, 2002)

Table 2: Environmental distribution of this substance using the fugacity model (level Ⅲ) under three emission scenarios

	Release: 100 % to air	**Release: 100 % to water**	**Release: 100 % to soil**
Air	0.0 %	0.0 %	0.0 %
Water	41.9 %	99.6 %	33.5 %
Soil	58.0 %	0.0 %	66.4 %
Sediment	0.2 %	0.4 %	0.1 %

A combined GLP study according to OECD Test Guideline 301C and OECD Test Guideline 302C showed that this substance was inherently biodegradable (MITI, 1997). On the other hand, the outcome of modified OECD screening test [OECD 301E] showed that methacrylamide was readily biodegradable (Roehm GmbH, 1988a). Although it was not GLP-compliant, the result was also reliable since this study was well conducted and documented. Hence the result from OECD 301E study should not be excluded. In conclusion, this substance should be regarded as readily biodegradable based upon the OECD 301E study.

Guide line	**% of biodegradation**	**Incubation period**	**Remark**
OECD 301C	24%(BOD) 31%(HPLC) 32%(TOC)	28 days	Inherently biodegradable
OECD 302C	95%(TOC) 100%(HPLC)		
OECD 301E	97%(DOC)	28 days	Readily biodegradable

The substance has low hydrophobicity (log Pow; -0.15), which indicates it has quite a low bioconcentration potential to aquatic organisms. A calculated value for BCF is 0.45 according to Lyman's method (Lyman W.J., et al, 1982).

At the production sites, waste and residues of the production process are incinerated (Roehm GmbH & Mitsui Chemicals). Wastewater is re-used partially for production. At the polymerization sites, the polymerization process is completed before releasing wastewater to a sewage treatment plant. This substance is readily biodegradable and has a low bioconcentration potential. Therefore the release of this substance to the aquatic environment is estimated to be very low.

The concentrations of methacrylamide in the influent and effluent of a sewage treatment plant and river water were measured. Sampling and measurement were conducted once at each site. The

highest concentration of methacrylamide monitored in wastewater from the factory was 2100 mg/L, however the concentration of this substance in the effluent of the sewage treatment plant was 0.2-0.3 mg/L-, which suggests a high removal rate in the plant. Methacrylamide is highly water soluble and its vapor pressure is low, hence the extent of adsorption to sludge and volatilization are expected to be low, which suggests that most of the removal of this substance in the wastewater treatment plant is due to biodegradation. Methacrylamide was detected at levels of n.d.-0.8 mg/L and n.d.-0.3 mg/L respectively in the river water collected at the points of ca. 50 and ca. 400 meters downstream from the outfall of the industrial site. Concentration of this substance in the river water at the point of ca. 50 meters upstream from outfall was below the limit of detection (n.d.; not detected, the limit of detection = 0.1 mg/L) (Mitsui Chemicals, 2002). Higher concentration was detected 50 meters downstream than in the effluent of the sewage treatment plant. Each sampling was not performed at the same time. Therefore variations of concentration greater than 0.8 mg/L in the effluent of the sewage treatment plant might occur occasionally. In conclusion, all environmental concentrations monitored were below 1 mg/L.

Sampling site	**Conc.(mg/L)**	
	01 July 2002	**08 July 2002**
River water		
ca.50m upstream from the outfall	-	<0.1
ca.50m downstream from the outfall	0.8	<0.1
ca.400m downstream from the outfall	0.3	<0.1
ca.5000m downstream from the outfall	-	<0.1
Effluent of sewage treatment plant	0.3	0.2
Influent of sewage treatment plant		
waste water line1	12	-
waste water line2	2100	-

-: Not available

Limit of detection: 0.1mg/L

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure at production sites may occur through dust by inhalation and by the dermal route. The end-product is in the form of granules of ca. 1mm diameter, however the powder is generated during the production process.

The atmospheric concentrations measured at the production plant in Japan are shown in table 3 (Mitsui Chemicals, 1990 and 2002).

EHE inh (Estimated Human Exposure by inhalation) is calculated using the maximum dust level measured at the production plant, a respiratory volume of 1.25 m^3/hr, an exposure period as outlined in table 2 and workers' body weight of 70kg.

EHE inh (total for sampling and analysis) = 4.19×10^{-3} mg/kg/day

EHE inh (monitoring of packing process) = 4.0×10^{-2} mg/kg/day

Operators who are engaged in sampling and analysis never monitor the packing process. Furthermore, workers operate with respiratory protective equipment and the EHE was calculated based on maximum data, hence the calculated EHE inh (monitoring of packing process) should be regarded as a worst case.

EHE der is calculated using a workers' body weight of 70 kg, an exposed skin surface area of 840 cm^2, an exposure period as outlined in Table 3 and an assessment factor (absorption rate) of 0.1(mg/cm^2/day). Workers wear helmets, goggles and masks, and their arms are fully covered with working clothes at all times. Workers have to put on gloves when sampling.

EHE der (total for sampling and analysis) = 0.177 mg/kg/day

EHE der (monitoring of packing process) = 0.6 mg/kg/day

Table 3: Monitoring data for methacrylamide at the production plant

Operation	Monitoring Data(mg/m^3)[a)]		Working Time (hours/day)	EHE(mg/kg/day) [b)]
	Maximum	Minimum		
Sampling for process evaluation	0.93 (in 2002)	0.79 (in 2002)	0.033	EHE inh = 5.48×10^{-4} EHE der = 4.95×10^{-3}
Analysis for process evaluation	0.18 (in 2002)	0.07 (in 2002)	1.0	EHE inh = 3.21×10^{-3} EHE der = 0.15
Sampling for product evaluation	0.16 (in 2002)	0.13 (in 2002)	0.15	EHE inh = 4.29×10^{-4} EHE der = 2.25×10^{-2}
Total for sampling and analysis				EHE inh = 4.19×10^{-3} EHE der = 0.177
Monitoring of packing process	0.56 (in 1990)	0.06 (in 2002)	4	EHE inh = 4.0×10^{-2} EHE der = 0.6

Note: a) Monitoring method:

Air at working place was drawn through liquid (water or 2% acetonitrile of phosphate buffer). Combinations of sampling rate-volume were 15L/minute-900L (in 1990) or 1L/minute-30L (in 2002). Absorbed substance was analyzed by GC (in 1990) or HPLC (in 2002). Sampling and analysis were conducted 3 to 6 times per location.

b) EHE was calculated based on maximum monitoring data.

2.3.2 Consumer Exposure

This substance is used as a raw material for polymerized compounds which are used as textile-finishing agents, paper finishing agents, coating agents, condensing agents, etc. Residual monomer content of the polymers is ca. 0.5% or less. (Mitsui Chemicals, 2001). Typical residual monomer contents are 0.001% to 0.01% (Roehm GmbH information). Migration of residual unpolymerised methacrylamide from polymer articles is very low, as shown in migration experiments into food simulants under EEC food regulations for plastic materials (Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs). Migration experiments for food contact approval in Europe were performed with the following food simulants under the conditions as listed below:

1. Deionised water, 10 days at 40°C and 2 hours at 70 °C
2. 3 % acetic acid, 10 days at 40°C and 2 hours at 70°C

3. 15 % ethanol, 10 days at 40°C and 2 hours at 70°C
4. Isooctane, 2 days at 20°C and 0.5 hour at 40°C

   (Isooctane is used as a replacement for vegetable oil for analytical reasons)

The migration of residual methacrylamide from plastic materials for food contact is very low under these conditions. The Specific Migration Limit (SML) is below 0.02 mg/kg (below 0.02 mg of methacrylamide in 1 kg food simulant) (Directive 90/128/EEC) (Roehm GmbH information, 2002).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

An experiment on distribution and excretion of methacrylamide was conducted by Hashimoto (1985a).

Distribution and excretion of ^{14}C-methacrylamide was studied in male rabbits after i.v. administration (15 % in water). Most of the radioactivity (86 % of the dose) was excreted with the urine within 24 hours. Expired ^{14}C-CO_2 was very low (1 %). After 24 hours i.v. administration to male rabbits, the highest concentration of radioactivity in the body was found in the liver, followed by serum, kidney, total blood and muscle.

Following 15 to 30 minutes dermal exposure to male rabbits, 23 to 52% of the administered radioactivity was excreted with urine within 24 hours. On the other hand, only 3.7 to 5.7% of the radioactivity was excreted in the urine of male rats after 24 hours following 15 to 30 minutes dermal exposure.

In vitro Studies

An in vitro study regarding the metabolism of methacrylamide demonstrated that phenobarbital induction increased the reaction rate about 2-fold suggesting a cytochrome P-450 dependent metabolism. (Tanii, 1981)

3.1.2 Acute Toxicity

Studies in Animals

Acute toxicity studies are listed in Table 4. All of the oral LD_{50} values to rats listed are greater than 1000 mg/kg. On the other hand, oral LD_{50} values to mice are 451 - 567 mg/kg. LD_{50} values to mice by other routes (i.p., s.c. and i.v.) are 200 – 500 mg/kg. The intraperitoneal LD_{50} to rats was 1300 mg/kg. Species difference may exist in terms of sensitivity to acute toxicity. Neurotoxic symptoms were observed in some acute toxicity studies.

Inhalation

A preliminary repeated dose inhalation toxicity study (Berufsgenossenschaft der Chemischen Industrie, 1998) can serve as a basis for an acute toxicity study. Male rats were exposed to methacrylamide for 6 hours/day, 7days/week at the concentration levels of 0.030, 12.8, 62.6 and 286 mg/m^3 (analytical concentration). No test substance effects were seen with respect to clinical observation, body weights, food consumption, grip strength, organ weights, macroscopic or microscopic examinations.

Dermal

One result for acute dermal toxicity to rats was provided. (BASF AG, 1966) In this study, 20% or 10% solution of methacrylamide was applied for 4 hours to abdominal skin. No motility was observed. Though temporary apathy were noted, these signs were also found in the control group. The estimated LDL_0 was greater than 1600mg/kg. However the reliability of this result is limited.

Oral

Among the results listed in Table 4, two oral rat studies (MHW, Japan, 1999a and Roehm, 1986)[OECD 401] were identified as the key studies because they were well conducted according to GLP and described in detail.

In the first key study conducted by MHW, methacrylamide was studied for oral toxicity in rats in a single dose toxicity test at the doses of 0, 1315, 1512, 1739 and 2000 mg/kg for both sexes. Deaths occurred in both sexes at 1512 mg/kg and higher. Staggering gait, salivation, irritability, soiled perioral fur, sitting position (hanging from the forelimb on the floor) and orange yellow urine were found in males and females at 1512 mg/kg and higher. Tremor was found in males and females at 1315 mg/kg and higher. Decrease in body weight was noted in males and females at 1315 mg/kg and higher. As for histopathological lesions, changes in testes and epididymides were observed in males at 1512 mg/kg and higher. Necrosis of neurocyte cells in the cerebellum was observed at 1315mg/kg and higher in both sexes. Degeneration of sciatic nerve fibers was observed in males at 1512 mg/kg and in females at 1739 mg/kg.

The LD_{50} values were 1789 mg/kg for males and 1774 mg/kg for females.

In the second key study (Roehm GmbH, 1986), oral LD_{50} values were 1938 mg/kg for males and 1653 mg/kg for females which were close to the ones obtained in the above study conducted by MHW. In this study, methacrylamide was administered to Wistar rats at doses of 1000, 2000 and 3000 mg/kg. Mortality was noted at 2000mg/kg and higher in both sexes. Sedation was observed at 1000 mg/kg and higher in both sexes. Ruffled fur was observed in females at 1000 mg/kg and higher and in males at 2000 mg/kg. At 2000 mg/kg and higher, ataxia, ventral body position and curved body position were noted in both sexes. Somnolence was observed only at 2000 mg/kg in both sexes. Emaciation was found in females at 2000 mg/kg. At the highest dose, latero-abdominal position was observed in both sexes and lacrimation was observed in females.

Both studies were conducted properly according to the guideline and GLP. No significant difference in LD_{50} was observed between them. However, the study by Roehm was performed with fewer dose levels in wider ranges compared to the test by MHW. Furthermore, histological examination was also performed in the MHW study. Therefore the MHW study is expected to provide more comprehensive information. Thus, further assessment should be conducted mainly based on the results from the MHW study.

Oral LD_{50} values for acrylamide that has a similar structure compared to methacrylamide were 175 – 203mg/kg. Neurotoxic effects were observed. Oral LD_{50} values of methacrylamide were higher than those of acrylamide. (European Commission, 2002)

Studies in Humans

There is no available information on humans.

Table 4: Acute toxicity of Methacrylamide in experimental animals

Route	Animals	Values	Type	References
Oral				
	Rats	1789 mg/kg for males 1774 mg/kg for females	LD_{50}	MHW, Japan,1999
	Rats	1938 mg/kg for males 1653 mg/kg for females	LD_{50}	Roehm, 1986
	Rats	1538 mg/kg	LD_{50}	Porokhova LA, 1980
	Rats	1223 mg/kg	LD_{50}	Strizhak EK, 1967 Leslie N,1976
	Rats	1380-1950 mg/kg	LD_{50}	BASF AG,1963
	Rats	1750mg/kg	LD_{50}	Rohm and Hass,1957
	Rats	ca. 1500mg/kg	ALD_{50} [1)]	BASF AG,1967
	Mice	475 mg/kg	LD_{50}	Strizhak EK, 1967 Leslie N,1976
	Mice	567 mg/kg	LD_{50}	Porokhova LA, 1980
	Mice	451 mg/kg	LD_{50}	Hashimoto K, 1981 RTECS,1997
	Mice	250-2500 mg/kg	LD_{100}	Roehm GmbH, 1979
	Rabbits	1865 mg/kg	LD_{50}	Strizhak EK, 1967 Leslie N,1976
	Cats	100-1000 mg/kg	ALD_{50} [1)]	BASF AG, 1967
Dermal				
	Rats	>1600 mg/kg	LDL_0	BASF AG, 1966
Others				
i.p.	Mice	200 mg/kg	LD_{50}	NTP,1990
i.p.	Mice	200-1200 mg/kg	LD_{100}	Roehm GmbH, 1979
i.p.	Rats	ca. 1300 mg/kg	ALD_{50} [1)]	BASF AG,1967
i.p.	Mice	ca. 450 mg/kg	ALD_{50} [1)]	BASF AG,1955
s.c.	Mice	ca. 500 mg/kg	ALD_{50} [1)]	BASF AG,1967
i.v.	Mice	360 mg/kg	ALD_{50} [1)]	BASF AG,1967

1) ALD_{50}: approximate lethal dose

Conclusion

LD_{50} values by oral exposure routes in rats were 1789 - 1938 mg/kg (males), 1653 - 1774 mg/kg (females). Clinical signs (e.g. staggering gait) and histopathological changes (e.g. degeneration of sciatic nerve) related to neurotoxicity were noted. Histopathological changes in testes and epididymides were also observed.

3.1.3 Repeated Dose Toxicity

Repeated dose toxicity results are shown in Table 5. Various procedures such as dosing manner or endpoints were designed in those studies. Clinical signs that suggested neurotoxicity of

methacrylamide appeared in many cases in rodents. In some of those cases, histopathological changes related to neurotoxicity were observed. Tendency for reduced mobility of spermatozoa and dystrophic changes in the liver and brain were noted in a 16 weeks repeated dose inhalation toxicity study in rats (Poroknova L.A., 1980). The reliability of this study is limited. Neurotoxicological symptoms were also observed in a few studies in rabbits and cats such as paralysis, splaying and forward extension of hindlimbs, etc. However the reliability of those studies is limited. (BASF AG, 1967a-b & Rohm and Haas, 1975)

Among the studies reported, three studies were selected as key studies.

The first study was a 28 days repeated dose toxicity study by MHW (MHW, Japan, 1999b). This study was conducted according to OECD TG 407 and GLP. This report was well documented. The other two studies were conducted by Aratani (1993). These studies were well conducted and documented, and had the longest administration period (12 months).

In the first study, methacrylamide was administered to three groups, each 7 males and 7 females, of Sprague-Dawley (Crj: CD) rats at doses of 0 (vehicle; purified water), 30, 100 and 300 mg/kg/day for 28 days. No animals died. In males at 300 mg/kg/day and females at 100 mg/kg/day and higher, the body weight gain was decreased. In both sexes at 300 mg/kg/day, a decrease in food and water consumption was noted. Males and females at 300 mg/kg/day showed staggering gait starting at day 20 or 21 of administration. Regarding functional observation, males and females at 300 mg/kg/day showed a decrease in muscle tone and ataxia. In males at 300 mg/kg/day, a decrease in grip strength was noted. Males at 100 mg/kg/day and higher and females at 30 mg/kg/day and higher showed a decrease in locomotor activity. These functional changes were observed continuously throughout the recovery period. Histopathological examination revealed degeneration of sciatic nerve fibers and axonal swelling in the cerebellar peduncle in males and females at 300 mg/kg/day. In males at 100 mg/kg/day and higher, a decrease in hemoglobin and MCH (mean cell hemoglobin) were noted. Males at 300 mg/kg/day showed a decrease in hematocrit, alpha1-globulin, alpha2-globulin and ALP (alkaline phosphatase), and an increase in albumin. In females at 300 mg/kg/day, a decrease in hematocrit, hemoglobin, alpha1- globulin, urea nitrogen, creatinine and ALP, and an increase in albumin and triglyceride were noted.

At the end of the recovery periods, males at 300 mg/kg/day showed an increase in absolute and relative organ weight of the testes.

The NOAELs were considered to be 30 mg/kg/day for males and below 30 mg/kg/day for females because the NOAEL for females was not determined in this study.

In the studies by Aratani (1993), methacrylamide was administered to four groups of 18-22 male Wistar rats or ddY mice by drinking water for 4, 8 or 12 months at doses of 0, 200, 400, 800 or 1200 ppm (equivalent to ca. 4.6, 9.1, 19.5, and 31.6 mg/kg/day for rats and ca. 24.3, 49.6, 120, and 220 mg/kg/day for mice). The equivalent doses mentioned above are re-calculated because the original doses in the literature by Aratani were apparently incorrect. The re-calculation manner is outlined in Appendix 3.

<Rats> At 800ppm (19.5mg/kg/day) and higher, the rotarod performance was reduced and a distension of the urinary bladder was observed. A 50% decrease in the rotarod performance was noted after 2 months and a half of administration at the highest dose. At the highest dose, symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait were seen. Serum total cholesterol and phospholipid content were increased significantly at the highest dose. Paralysis of hindlimb related to neurotoxicity was observed starting on the 15^{th} week of administration at 1200ppm (31.6mg/kg/day). As for histopathological observations, shrinkage and loss of myelinated fibers of the sciatic nerve and atrophy of the gastrocnemius muscle were observed at 800ppm (19.5mg/kg/day) and higher.

The NOAEL for rats in this study was considered to be ca. 9.1 mg/kg/day (400ppm).

<Mice> At 800ppm (120mg/kg/day) and higher the rotarod performance was reduced and a distension of the urinary bladder was observed. A 50% decrease in the rotarod performance was noted at 3 weeks of administration at the highest dose. At 800ppm (120mg/kg/day) and higher, symptoms of peripheral neuropathy including a decrease in grip strength and abnormal gait were seen and the body weight gain was decreased. At 400ppm (49.6mg/kg/day) and higher, paralysis of hindlimb was observed. Paralysis of hindlimb related to neurotoxicity was observed starting on the 10^{th} week of administration at 1200ppm (220mg/kg/day). As for histopathological observations, shrinkage and loss of the myelinated fibers of sciatic nerve was observed at 400ppm (49.6mg/kg/day) and higher and atrophy of the gastrocnemius muscle was observed at 800ppm (120mg/kg/day) and higher.

The NOAEL for mice in this study was considered to be ca. 24.3 mg/kg/day (200ppm).

Neurotoxicological signs were observed in acrylamide repeated dose animal studies (primates, dogs, cats and rodents) as well as degenerative changes in peripheral and optic nerves, and degeneration of the lateral geniculate nucleus. A clear NOAEL for neurotoxicity of 0.5 mg/kg/day was provided from a 2-year rat carcinogenicity study by drinking water in which slight peripheral nerve lesions were seen in the absence of any clinical signs of toxicity.

As mentioned above, the 1-year drinking water study in rats with methacrylamide yielded a NOAEL of ca. 9.1 mg/kg/day . The NOAEL for acrylamide is 18 times lower than that for methacrylamide for repeated dose toxicity in rats. However, the two studies were not conducted according to the same protocol such the as application period.

Conclusion

In the 28 days repeated dose oral toxicity test [OECD TG 407], the NOAELs (gavage, rats) were considered to be 30 mg/kg/day for males and below 30 mg/kg/day for females. Neurotoxic effects were demonstrated at the doses below the guidance values (GHS) for this study. In a 12 months repeated dose toxicity study by drinking water, NOAELs were considered to be ca. 9.1mg/kg/day for male rats and ca. 24.3mg/kg/day for male mice. In these studies, decrease in locomotor activity or rotarod performance, and clinical signs such as paralysis of hindlimb, decrease in grip strength and abnormal gate related to neurotoxicity were noted. A 50% decrease in the rotarod performance was noted at 3 weeks of administration at the highest dose in mice. Male and female rats at 300mg/kg/day showed staggering gait starting on day 20 or 21 of administration. Degeneration of sciatic nerve fibers, axonal swelling in the cerebellar peduncle and atrophy of gastrocnemius muscle were observed histophathologically.

Based upon the above discussions, it can be concluded that methacrylamide has neurotoxic effects.

Table 5. Repeated dose toxicity of methacrylamide in experimental animals

Route	Animal	Period and dose	Results	Type	Neurotoxic effect	Reference
ORAL						
Gavage	Rats (male/ female)	28 days 30- 300 mg/kg	30 mg/kg (male) <30 mg/kg (female)	NOAEL	Observed	MHW,1999
Feed	Rats (male)	25 days 50 mg/kg (11 days) 100 mg/kg (next 14 days)	No neurotoxic effects	Clinical signs and functional test	Not observed	Barnes JM,1970 Leslie N,1976
Drinking water	Rats (male)	60-90 days 6.93- 23.5 mM	10.4 mM	NOAEL	Observed	Tanii H,1983
Drinking water	Rats (male)	12 months ca.4.6- 31.6 mg/kg	ca.9.1 mg/kg	NOAEL	Observed	Aratani J,1993
Drinking water	Mice (male)	12 months ca.24.3- 220 mg/kg	Ca.24.3 mg/kg	NOAEL	Observed	Aratani J,1993
Unspecified	Rats (male/ female)	35 or 95 days 360- 380 mg/kg (35 days) 43- 44 mg/kg (95 days)	43 mg/kg	NOAEL	Observed	BASF AG,1967
Gavage	Mice (male/female)	14 days 125- 500 mg/kg	125 mg/kg	NOAEL	Observed	Roehm Gmbh,1979
Gavage	Mice (male)	8- 10 weeks 153 mg/kg (twice per week)	Treatment related changes were observed at 153 mg/kg	Clinical signs and functional test	Observed	Hashimoto K,1981 NTP,1990
Gavage	Rabbits (male /female)	10 1/2 weeks 100- 500 mg/kg (5days per week)	<100mg/kg	NOAEL	Observed	BASF AG,1967

Table 5. Repeated dose toxicity of methacrylamide in experimental animals (Continued)

Route	Animal	Period and dose	Results	Type	Neurotoxic effect	Reference
ORAL						
Gavage	Cats (male/ female)	9 weeks 100 mg/kg (4- 45 times) 250mg/kg (3- 6 times) 500mg/kg (2 times)	<100MG/KG	NOAEL	Observed	BASF AG,1967
INHALATION						
	Rats	16 weeks 3.2-34.5 mg/m^3	3.2 MG/M^3	NOAEL	Unspecified	Porokhova LA,1980 Meshcheryakova SA,1983
DERMAL						
	Rabbits (male)	4 weeks ca.700- 800 mg/kg 21 times (5 days per week;8 hours per day)	ca. 700 mg/kg	NOAEL	Not observed	BASF,1966
	Rabbits (male/female)	5 weeks or 12 weeks 5,50 mg/kg (12 weeks) 500 mg/kg (5 weeks)	50 mg/kg	NOAEL	Observed	Rohm and Hass,1975
	Guinea pig	4 weeks 1000 mg/kg 20 times (5 days per week, 24 hours per day)	Not obtained	NOAEL	Unspecified	BASF,1966

3.1.4 Mutagenicity

Five genetic toxicity studies were reported, which are shown in Table 6.

Table 6: Summary of genotoxicity studies of methacrylamide

Type of test	Test system	Dose	Result	Reference
Bacterial test				
Ames test *(reverse mutation)*	*S. typh.* (strains TA98, TA100,TA1535,TA1537,TA 1538)	Up to 5,000 ug/plate	Negative (+ & -MA※)	Hashimoto K. (1985b)
	S. typh. (strains TA98, TA100,TA1535,TA1537) *E. coli* WP2 uvr A OECD TG 471	Up to 5,000 ug/plate	Negative (+ & -MA※)	MHW, Japan (1999c)
Non-bacterial in vitro test				
Chromosomal aberration test	CHL/IU cells OECD TG 473	Up to 5000 ug/mL (58.7mM)	Positive (- MA※)	Mitsui Chemicals (1993)
	CHL/IU cells OECD TG 473	Up to 900 ug/mL (10mM)	Negative (+ & - MA※)	MHW, Japan (1999d)
In vivo test				
Dominant lethal assay	Mouse(CD-1) Part of modified reproductive assessment by continuous breeding protocol	Up to 240ppm (corresponding to 49 mg/kg/day)	Negative	NTP(1992) Chapin R.E. (1995)

※:metabolic activation

In vitro Studies

Bacterial test

The study by MHW Japan, (1999c) was well conducted and reported according to guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 471 and GLP, hence it is regarded as a key study. All results were negative up to 5,000 ug/plate in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2 uvrA with and without an exogenous metabolic activation system, which was consistent with the outcome of another mutagenicity study conducted by Hashimoto (1985b).

Non-bacterial test

The chromosomal aberration study with CHL cells by MHW, Japan (1999d) was identified as a key study because this study was conducted according to GLP and well documented. [Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) & OECD TG 473] In this study,

methacrylamide did not induce chromosomal aberrations under any treatment up to 900 ug/mL (10mM).

A positive result was reported in another chromosomal aberration study (Mitsui Chemicals, 1993). This study was performed according to GLP and Japanese guidelines for screening mutagenicity testing of chemicals, however the concentration in which positive response was detected exceeded the maximum exposure level (10mM). Therefore the positive response should not be regarded to reflect a specific mutagenicity of the test substance.

In vivo Studies

A dominant lethal assay with mice was conducted as a part of a reproductive toxicity assessment with the continuous breeding protocol (NTP, 1992 & Chapin R.E., 1995). Methacrylamide was tested at the levels of 24, 80 and 240 ppm in drinking water corresponding to 4.5 – 49 mg/kg/day for reproductive evaluation. Males after treatment of methacrylamide for approximately 100 days cohabited with untreated females for four nights (maximum). No dominant lethal effect (increase in the number of early resorptions/female, the number of dead fetuses, or in total postimplantation loss) was observed.

Acrylamide was negative in standard bacterial assays, however, this substance was clastogen in vitro. In the case of germ cells, positive results were observed in a number of different germ cell assays; chromosome aberrations, micronucleus assays, UDS, dominant lethal assays, heritable translocation and specific locus assays. Thus, acrylamide is genotoxic in vivo. (European Commission, 2002)

Conclusion

Methacrylamide was not mutagenic in bacteria [OECD TG 471] and not clastogenic in CHL/IU cells [OECD TG 473]. A negative result was also obtained in a dominant lethal assay. Namely, methacrylamide did not demonstrate a genotoxic potential in these studies. However, acrylamide having a similar structure compared to methacrylamide is clearly a genotoxic compound.

3.1.5 Carcinogenicity

Two studies for evaluating the tumor activity of methacrylamide were reported.

In the first study, methacrylamide was given intraperitoneally to mice either once a day or once every other day for 5 times at the dose of 200 mg/kg. (Matsuda, 1989) During the 6 months observation period, necropsies and histopathological observations were conducted periodically. Total numbers of animals in which lung tumor formation was observed were significantly higher (the former group: 16 out of 57; 28%, the latter group: 8 out of 38; 21%) than that of control (1 out of 48; 2.1%). However, this study was not conducted according to GLP and dose dependency was not clear because methacrylamide was administered at one dose level. Descriptions about animal husbandry including barrier system were not reported. Therefore the reliability of this study was considered to be limited.

The second study was conducted by BASF (Roehm GmbH, 1990). In this study, methacrylamide was tested for tumor initiating activity. First, mice received methacrylamide at 0, 25, 50 and 100 mg/kg and acrylamide at 50 mg/kg 6 times by gavage for 2 weeks (initiation period). At the end of initiation period the animals were kept untreated for 2 weeks and the promotion period began. During the promotion period, dermal application of TPA (12-o-tetra-decanoylphorbol-13-acetate) that was a known tumor promoter was conducted at 0 or 2.5 ug/body weight 60 times for 20 weeks. After the promotion period, the animals remained untreated for 28 weeks and were sacrificed. No increased numbers of neoplasm were seen in the methacrylamide treatment groups with and without

TPA. Therefore methacrylamide had no tumor initiating activity in this study. However, some doubts can be raised concerning the validity and reliability of the test system as acrylamide that had previously been reported to have initiating properties in a study conducted following the same protocol did not show a tumor initiating potential in this study. Although this study was well conducted under GLP and well documented, reliability of this study was considered to be limited.

Conclusion

Two-year administration studies in males and females F344 rats clearly demonstrate that acrylamide is carcinogenic in rats. (European Commission, 2002) As for methacrylamide, positive and negative effects on tumorgenisis were obtained from 2 studies. However, the reliability of these studies was limited, therefore these studies should not be regarded as definitive. In conclusion, the data are insufficient to judge the carcinogenicity potential of this chemical.

3.1.6 Toxicity for Reproduction

Studies in Animals

Three studies were conducted to evaluate reproductive/developmental toxicity of methacrylamide. These studies were conducted according to GLP and well-designed protocols (OECD 421, modified design of the National Toxicology Program's Reproductive Assessment by Continuous Breeding Protocol; RACB and a established protocol similar to OECD TG 414), which gave detailed information.

Although the three studies were well conducted and documented, based on the weight-of-evidence-approach, the last two studies were more significant because the first study was for screening.

Reproductive toxicity

The first study was conducted according to OECD TG 421 (MHLW, Japan, 2001). In this study methacrylamide was administered to three groups, each 13 males and 13 females of Sprague-Dawley (Crj: CD) rats at doses of 0 (vehicle: purified water), 12.5, 50 and 200 mg/kg/day, respectively. Males were dosed for 42 days and females were dosed from 14 days before mating, throughout pregnancy to day 3 of lactation. Deaths occurred in one male and 4 females at 200 mg/kg/day. One female was sacrificed on becoming moribund at 200 mg/kg/day. Dragging of hindlimb appeared in all animals at 200 mg/kg/day. Body weight gain was decreased at 50 and 200 mg/kg/day. Food consumption was also decreased in males at 50 and 200 mg/kg/day and in females at 200 mg/kg/day. Although a low incidence of pneumonia was observed at 200 mg/kg/day, the reproductive organs were not affected in either sex in histopathological observation. Fertility and estrous cyclicity were not affected, but the copulation rate was decreased at 200 mg/kg/day. Delayed parturition and abnormal nursing, and low body weights and decreased viability of the pups were also observed at 200 mg/kg/day. No external anomaly was found in any pups.

The NOAEL for systemic toxicity is considered to be 12.5 mg/kg/day in male and female rats. The copulation rate was decreased and delayed parturition and abnormal nursing were noted at 200 mg/kg/day. Furthermore, low body weights and decreased viability of the pups was noted at 200mg/kg/day.

50 mg/kg/day was considered to be the NOAEL for reproductive and developmental toxicity in this study. However, effects in pups were seen at maternally toxic doses, therefore these changes might be related to severe maternal systemic toxicity.

The second study was conducted according to the modified RACB protocol. Male and female Swiss CD-1 mice were provided drinking water containing methacrylamide (24, 80 and 240 ppm

corresponding to 4.5, 15,4 and 49 mg/kg/day) and mated with the same treatment group. During the first 7 days, animals were dosed separately, followed by a 98 days dosing period. F_1 mice which were dosed at the same concentrations as F_0 mice (24, 80 and 240 ppm corresponding to 6.8, 23.8 and 71.3 mg/kg/day), were mated from PD21 to 74(±10) days. Reproductive performance and grip strength (as indicator for neurotoxicity) were evaluated, and necropsy and histopathological data were collected in F_0 and F_1 generations. Moreover a dominant lethal study was conducted on F_0 males. In the F_0 generation, no clinical or histopathological changes were observed. There was no effect on reproductive competence in the F_1 generation.

NOAELs for reproductive toxicity were considered to be 49 mg/kg/day for F_0 and 71.3 mg/kg/day for F_1 (NTP, 1992 & Chapin R.E., 1995).

Reproductive organs were not affected in 2 key studies for reproductive toxicity. On the other hand, changes in testes and epididymis such as decrease of spermatozoa were observed in high dose groups (1512 mg/kg and higher) in which deaths occurred in an oral acute toxicity study. (MHW, Japan, 1999a) Changes in testes such as tendency for reduced mobility of spermatozoa were also noted in a 16 weeks repeated dose inhalation toxicity study in rats (Poroknova L.A., 1980), however these results were equivocal since the reliability of this study was limited.

The reproductive toxicity of acrylamide was evaluated according to the modified RACB protocol. The NOAEL of acrylamide for reproductive toxicity was about 9 mg/kg/day (European Commission 2002), which was lower than that of methacrylamide.

Developmental Toxicity

Pregnant female (Swiss CD-1) mice were dosed daily by gavage with this substance from GD (Gestational days) 6 to GD17 to evaluate developmental toxicity. Dose levels (60, 120 and 180 mg/kg/day) were chosen based on a previously conducted study with acrylamide. All animals were killed on GD17 and examined for maternal body weight, implant status, fetal weight, sex and morphological development. No treatment-related maternal mortality was observed. Maternal body weight on GD17, maternal weight gain during treatment and gestation, and corrected maternal weight gain was decreased at 180 mg/kg/day. Relative maternal liver weight was increased at 120 mg/kg/day and higher; gravid uterine weight was decreased at 180 mg/kg/day. The maternal NOAEL was considered to be 60 mg/kg/day.

Mean fetal body weight was reduced at 120 mg/kg/day only with a little increase in maternal relative liver weights. It was considered that the decrease in mean fetal body weight resulted from specific developmental toxicity. At 180 mg/kg/day, increased postimplantation death per litter and decrease in mean fetal body weight were observed. Morphological development was not affected.

The NOAELs for developmental toxicity was considered to be 60 mg/kg/day. (NTP, 1990 & George J.D., 1998)

In the reproductive toxicity study according to the RACB protocol mentioned above, reduced forelimb grip strength was observed in three-week-old F_1 male offspring at 80 ppm (23.8 mg/kg/day) and 240 ppm (71.3 mg/kg/day). Hindlimb grip strength was reduced in three-week-old male and female offspring at 24 ppm and higher, which indicated neurotoxic effects of this substance. However these effects became insignificant when the animals grew older at 24 ppm (6.8 mg/kg/day) and 80 ppm(23.8 mg/kg/day). Decrease in hindlimb grip strength was observed in 16 week-old female F_1 offspring at 240 ppm (71.3 mg/kg/day). Though the toxicological significance of this change in 16 week-old offspring was equivocal, it was considered that the recovery from the neurotoxic effect might not be completed in the high dose group.

The NOAEL was considered to be less than 6.8 mg/kg/day (24 ppm) in terms of developmental toxicity (NTP, 1992 & Chapin R.E., 1995).

Studies in Humans

There is no available information on humans.

Conclusion

Reproductive toxicity

In the first screening test [OECD TG 421], the NOAEL was considered to be 12.5 mg/kg/day for maternal toxicity. On the other hand the NOAEL for reproductive and developmental toxicity was considered to be 50 mg/kg/day. However reproductive changes observed in this study might be related to severe maternal systemic toxicity. In the reproductive toxicity study according to the RACB protocol, no reproductive abnormality was noted. NOAELs for reproductive toxicity were considered to be 49 mg/kg/day for F_0 and 71.3 mg/kg/day for F_1 generation.

Developmental toxicity

In the developmental toxicity study, the NOAEL was considered to be 60 mg/kg/day for developmental toxicity because mean fetal body weight was reduced and increased postimplantation death per litter was observed. On the other hand, neurotoxic effects were observed in three-week-old male and female F_1 offspring at 24 ppm and higher in the two-generation reproductive toxicity study according to the RACB protocol. Those changes became insignificant at 24 and 80 ppm when the animals grew older. The NOAEL for developmental toxicity in this study was considered to be less than 6.8 mg/kg/day (24 ppm).

3.1.7 Other health information

Slight irritation to skin in rabbits was reported (Roehm GmbH, 1988b) [OECD TG 404]. In this study, the P.I.I. (Primary Irritation Index) calculated with the scores at 24, 48 and 72 hours after removing the test substance was 1.1. On the other hand, a different P.I.I. (0.0) was calculated with the scores at 24, 48 and 72 hours after removing the test substance from another study in which very slight erythema were observed at all treated skin areas one hour after patch removal (Mitsui Chemicals, 1998)[OECD TG 404]. Both studies were well conducted and documented according to GLP. Although the outcomes of the two studies are a little conflicting, they are both reliable. Hence methacrylamide should be regarded as not to slightly irritant to skin. As for acrylamide, no signs of skin irritation were observed in a well conducted study in rabbits, however, based upon human experience it appears that acrylamide is a skin irritant. (European Commission, 2002) Structure activity relationship between methacrylamide and acrylamide is not clear in terms of skin irritation.

Moderate irritation to eyes in rabbits was observed (Roehm GmbH, 1988c)[OECD TG 405]. This study was conducted and documented according to GLP, therefore the outcome of this study was reliable. The mean primary irritation score (1, 24, 48 and 72 hours) was 3.83. The mean scores for tested animals at each observation time (1, 24, 48 and 72 hours) were 1.00 for corneal opacity, 0.00 – 0.33 for iris, 1.33 – 2.33 for conjunctivae (redness) and 0.00 – 2.00 for conjunctivae (chemosis). Acrylamide was a clear eye irritant to rabbits (European Commission, 2002) as well as methacrylamide.

Two studies on skin sensitization were conducted. Both studies were without detailed documentation and their results conflicted mutually. Therefore they were not identified as key studies. Clear evidence that acrylamide is skin sensitizer is mentioned in the SIDS documents for

acrylamide (European Commission, 2002), however, there is currently no evidence to conclude whether methacrylamide is skin sensitizer or not.

Some in vitro studies were conducted to evaluate the neurotoxicity of methacrylamide. 25 mM of methacrylamide had no effect on the resting potential of the isolated desheathed sciatic nerve of the isolated retina of a frog. (Boehling H.G., 1977) Methacrylamide also had no effect on neurite-extending chick dorsal root ganglion (DRG) cells in terms of alterations in morphology and function up to 16.6 mM for 16 hours. (Martenson C. H., 1995) On the other hand, methacrylamide inhibited the neurite growth from rat dorsal root ganglion in culture. The half-maximum inhibition concentration was 30 mM. (Tanii H, 1991)

Information of structure-toxicity relationship

Acrylamide which has a similar structure to methacrylamide is a well known neurotoxic chemical. In this section, the neurotoxicity of acrylamide and methacrylamide is discussed. Neurotoxicity of acrylamide and methacrylamide in experimental animals is shown in Table 7.

The acute oral LD50 for rats of methacrylamide is higher than that of acrylamide, however neurotoxic symptoms were observed for both chemicals in acute oral toxicity studies. In the acute toxicity study with acrylamide, groups of 10 male F344 rats received single doses of 50, 100, 125, 200 or 250 mg/kg of test chemical and the decrease in hindlimb grip strength which was noted at 200 mg/kg attained statistical significance. As for methacrylamide, in the MHW studies (see 3.1.2. Acute Toxicity), histopathological changes related to neurotoxicity such as degeneration of sciatic nerve fibers were observed in males at 1512 mg/kg and in females at 1739 mg/kg.

In repeated dose toxicity studies, neurotoxic effects were observed for both acrylamide and methacrylamide. However the NOAELs for methacrylamide are higher than those for acrylamide. In a combined chronic toxicity/carcinogenicity study conducted according to modern protocol standards, groups of 90 male and 90 female F344 rats received 0, 0.01, 0.1, 0.5, 2 mg/kg/day acrylamide in drinking water for up to 2 years. At 2 mg/kg/day, histopathological observations related to neurotoxicity with slight peripheral nerve lesions were observed. On the other hand, in the study by Aratani (1993, see 3.1.3. Repeated Dose Toxicity) methacrylamide was administered to male Wistar rats by drinking water for 1 year. Histopathological observations related to neurotoxicity such as shrinkage and loss of myelinated fiber of sciatic nerve were observed at 800 ppm (ca. 19.5 mg/kg) and higher.

In a continuous breeding study, F1 male and female Swiss mice received 0, 0.86, 2.9, 7.7 mg/kg/day acrylamide in drinking water (Chapin, 1995). Decrease in forelimb grip strength was noted in 10 week-old F1 male offspring at 2.9 and 7.7 mg/kg/day. As for methacrylamide, a study conducted according to the modified RACB protocol (NTP, 1992; see 3.1.6. Reproductive/developmental Toxicity), a decrease in hindlimb grip strength was noted in 3 week-old F1 male and female offspring at 6.8 mg/kg and higher.

Table 7: Neurotoxicity of acrylamide and methacrylamide in experimental animals

	Animals	Acrylamide	Methacrylamide
Neurotoxicity on acute toxicity study			
Oral: LD_{50}	Rats	175 mg/kg (males) 203 mg/kg (females)	1789 – 1938 mg/kg (males) 1653 – 1774 mg/kg (females)
Remark		Decrease in hindlimb grip strength was noted at 200mg/kg attained statistical significance (males)	Histopathological changes related to neurotoxicity such as degeneration of sciatic nerve fibers were observed in males at 1512 mg/kg and in females at 1739 mg/kg
Neurotoxicity on repeated-dose toxicity study			
Oral (drinking water): NOAEL	Rats	0.5 mg/kg (males and females) (2 years study)	ca. 9.1 mg/kg (males) (1 year study)
Remark		Histopathological observations related to neurotoxicity with slight peripheral nerve lesions were observed in the absence of any clinical sign of toxicity at 2 mg/kg/day	Histopathological observations related to neurotoxicity neurotoxicological signs were observed at 800 ppm (ca.19.5 mg/kg) and higher
Neurotoxicity on reproductive toxicity study (2-generation)			
Oral (drinking water):	Mice	Decrease in forelimb grip strength was noted at 10 week-old F_1 male offspring at 2.9 and 7.7 mg/kg/day	Decrease in hindlimb grip strength was noted at 3 week-old F_1 male and female offspring at 6.8 mg/kg and higher

(European Commission, 2002 & Chapin, 1995)

3.2 Initial Assessment for Human Health

After i.v. administration of ^{14}C-methacrylamide to male rabbits, most of the radioactivity (86 % of the dose) was excreted with the urine within 24 hours. Following 15 to 30 minutes dermal exposure to male rabbits, 23 to 52% of the administered radioactivity was excreted with urine within 24 hours. On the other hand, only 3.7 to 5.7% of the radioactivity was excreted in the urine of male rats after 24 hours following 15 to 30 minutes dermal exposure. An in vitro study on the metabolism of methacrylamide demonstrated that phenobarbital induction increased the reaction rate about 2-fold suggesting a cytochrome P-450 dependent metabolism.

The values of oral LD_{50} to rats were obtained from two key studies [OECD 401]: 1789 mg/kg (males) and 1774 mg/kg (females) from one study, and 1938 mg/kg (males) and 1653 mg/kg (females) from the second study. Tremors, salivation, irritability, soiled perioral fur, sitting position and orange-yellow urine in cage trays, sedation, ataxia, somnolence, etc were found in the clinical observation. Histopathological changes were observed in the testes, epididymides, cerebellum and sciatic nerves.

This substance is not to slightly irritating based upon 2 reliable studies. As for eye irritation, it was moderately irritant to eyes in rabbit. There is no available information on skin sensitization.

In a 28 days repeated dose study with rats [OECD TG 407] by gavage at the dose levels of 0, 30, 100 and 300 mg/kg/day, body weight gain and food and water consumption were decreased in both sexes at 300 mg/kg/day. Body weight gain was also observed in females at 100 mg/kg/day. Some clinical and functional changes (decrease in muscle tone, ataxia and decrease in grip strength) were

found at 300mg/kg/day. Males at 100 mg/kg/day and higher and females at 30 mg/kg/day and higher showed a decrease in locomotor activity. These functional changes were observed continuously throughout the recovery period. Histopathological examination revealed degeneration of sciatic nerve fibers and axonal swelling in the cerebellar peduncle at 300 mg/kg/day in both sexes. At 300 mg/kg/day, a decrease in hematocrit, hemoglobin, MCH, urea nitrogen, creatinine, alpha1- globulin, alpha2-globulin and ALP, and an increase in albumin and triglyceride was noted. At 100 mg/kg/day, a decrease in hemoglobin and MCH was noted. At the end of the recovery period, absolute and relative testis weights increased.

The NOAEL for females could not be determined in this study. Therefore the NOAELs were considered to be 30 mg/kg/day for males and below 30 mg/kg/day for females.

In 12 months repeated dose toxicity studies with rats and mice, the NOAELs (drinking water) were considered to be ca. 9.1 mg/kg/day (400 ppm) for male rats and ca. 24.3 mg/kg/day (200 ppm) for male mice.

As for rats, at 800 ppm (19.5 mg/kg/day) and higher, reduction in the rotarod performance, distension of the urinary bladder, shrinkage and loss of myelinated fibers of sciatic nerve, and atropy of gastrocnemius muscle were observed. Symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait were noted at 1200 ppm (31.6 mg/kg/day). Serum total cholesterol and phospholipid content were increased significantly at 1200 ppm (31.6 mg/kg/day).

In mice, reduction in the rotarod performance, symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait, atropy of gastrocnemius muscle, and distension of the urinary bladder were seen at 800 ppm (120 mg/kg/day) and higher. At 800 ppm (120 mg/kg/day) and higher, body weight gain was decreased. At 400 ppm (49.6 mg/kg/day) and higher, paralysis of hindlimb, shrinkage and loss of myelinated fibers of sciatic nerve were observed.

The lowest NOAEL of repeated dose toxicity was considered to be ca. 9.1 mg/kg/day for male rats. In three studies, effects on functions and clinical signs, and histological changes related to neurotoxicity were noted.

Based upon the discussions above, methacrylamide has neurotoxic effects.

Methacrylamide was not mutagenic in bacteria [OECD TG 471] and not clastogenic in CHL/IU cells [OECD TG 473]. It also gave a negative response in a dominant lethal assay with mice conducted as part of a modified reproductive assessment. Males after treatment of methacrylamide (4.5 - 49 mg/kg/day) for approximately 100 days were cohabited with untreated females. No dominant lethal effects were observed. In conclusion, methacrylamide did not demonstrate a genotoxic potential in these studies. However, acrylamide having a similar structure to methacrylamide is clearly a genotoxic compound.

As for carcinogenicity, two studies for evaluating the tumor activity of methacrylamide were reported. In the first study, the ratio of lung tumor formation was significantly higher than that of the control, 6 months after 5 intraperitoneal administrations to mice at the dose of 200 mg/kg. However, the reliability of this study was limited.

No increased numbers of neoplasm were seen in the methacrylamide treatment groups with and without the tumor promoter TPA in the second study. In this study, methacrylamide at 0, 25, 50 and 100 mg/kg and acrylamide at 50 mg/kg were administered 6 times orally to mice. After this period, dermal application of TPA was conducted 60 times. Animals were sacrificed 1 year after the first application of methacrylamide. This study was well conducted under GLP and well documented. However acrylamide that had previously been reported to have initiating properties in a study

conducted following the same protocol, did not show a tumor initiating potential in this study. Hence the reliability of this study was considered to be limited.

In conclusion, the data are insufficient to judge the carcinogenicity potential of this chemical.

In Preliminary Reproduction Toxicity Screening Test by Oral Administration in Rats [OECD TG 421], this substance was examined at the dose levels of 12.5, 50 and 200 mg/kg/day. At 200 mg/kg/day, the copulation rate was decreased, delayed parturition and abnormal nursing were found. Low body weights and decreased viability of the pups were also observed at 200 mg/kg/day.

The NOAEL was considered to be 50 mg/kg/day for reproductive and developmental toxicity in this study. However effects in pups were seen at maternally toxic doses, therefore these changes might be related to severe maternal systemic toxicity.

A reproductive toxicity study on mice was conducted according to the modified RACB protocol (24, 80 and 240 ppm corresponding to 4.5 - 49 mg/kg/day for F_0 and 6.8 - 71.3 mg/kg/day for F_1). In both generations, this substance was negative for reproductive toxicity. No dominant lethal effect was observed on F_0 males.

The NOAELs for reproductive toxicity in this study was 49 mg/kg/day for F_0 and 71.3 mg/kg/day for F_1.

The lowest NOAEL for reproductive toxicity was considered to be 49 mg/kg/day.

Pregnant female mice were dosed (60, 120 and 180 mg/kg/day) daily by gavage with this substance from GD6 to GD17 to evaluate developmental toxicity. The maternal NOAEL was considered to be 60 mg/kg/day because relative maternal liver weight was increased at 120 mg/kg/day and higher, and maternal weight gain and gravid uterine weight were decreased at 180 mg/kg/day. Mean fetal body weight was reduced at 120 mg/kg/day only with a little increase in maternal relative liver weights. It was considered that the decrease in mean fetal body weight resulted from specific developmental toxicity. At 180 mg/kg/day, increased postimplantation death per litter and a decrease in mean fetal body weight were observed. Morphological development was not affected.

The NOAEL was considered to be 60 mg/kg/day for developmental toxicity because the mean fetal body weight was reduced at 120 mg/kg/day and higher.

In a reproductive toxicity study with mice according to the modified RACB protocol, a decrease in hindlimb grip strength was observed at 24 ppm (6.8 mg/kg/day) and higher in three-week-old male and female offspring that indicated neurotoxic effect, however that effect became insignificant when the animals grew older at 24 (6.8 mg/kg/day) and 80 ppm (23.8 mg/kg/day).

The NOAEL for developmental toxicity of this study was considered to be less than 6.8 mg/kg/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The results from acute and chronic toxicity tests with aquatic organisms are shown in Table 8.

Table 8: Aquatic toxicity of methacrylamide

Organism	Test method	Result (mg/L)	Reference
Micro organisms			
Green algae (*Selenastrum capricornutum*) ATCC 22662	OECD TG 201 72 hr (cl)	EC_{50} (bms) > 1000 (nc*) NOEC (bms) = 556 (nc*) EC_{50} (24-48,24-72, gr) > 1000 (nc*) NOEC (24-48,24-72, gr) > 1000 (nc*)	EA, Japan (2000a)
Bacteria (*Pseudomonas putida*)	DIN 38412 Teil 8 16 hr	EC_{10} > 10000 (nc)	Roehm GmbH(1988d)
Invertebrates			
Water flea (*Daphnia magna*)	OECD TG 202 48 hr (op,s)	EC_{50} (24 hr, imm) > 1000 (nc*) EC_{50} (48 hr, imm) > 1000 (nc*)	EA, Japan (2000b)
	OECD TG 211 21 day (op,ss)	LC_{50} for parents > 100 (nc*) NOEC (rep) > 100 (nc*) LOEC (rep) > 100 (nc*)	EA, Japan (2000c)
Fish			
Medaka (*Oryzias latipes*)	OECD TG 203 96 hr (op, ss)	LC_0 > 100 (nc*) LC_{50} > 100 (nc*) LC_{100} > 100 (nc*)	EA, Japan (2000d)
Goldorfe (*Leuciscus idus*)	DIN 38412 Teil 15 48 hr (op,s)	LC_0 = 933 (nc) LC_{50} = 2730 (nc) LC_{100} = 7989 (nc)	Roehm GmbH (1987)

<Abbreviation>

cl; closed system, op; open system s; static, ss; semi-static nc; nominal concentration (actual concentration not measured), nc; nominal concentration (actual concentration measured and greater than 80% of the nominal), bms; biomass, gr; growth rate, imm; immobility, rep; reproduction.*

The acute toxicity studies with Green algae [OECD TG 201], Daphnia [OECD TG 202], and fish [two species, OECD TG 203 & other method] were well conducted and documented.

The chronic toxicity studies to to Daphnia [OECD TG 211] and Green algae [OECD TG 201] were also well documented and conducted. Hence these five studies were identified as key studies and adopted for the calculation of a PNEC.

An acute toxicity study to bacteria (*Pseudomonas putida*) was not identified as a key study because no EC_{50} was calculated.

Four studies according to OECD testing guideline [201,202,203and 211] were conducted as limit tests.

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

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

Methacrylamide is readily biodegradable and estimated to have a quite low bioaccumulation potential because of its low log Pow (-0.15).

In acute toxicity studies, the EC_{50} (biomass) and EC_{50} (growth rate) for Green algae [OECD TG 201] were greater than 1000 mg/L, and the EC_{50} (immobility) for Daphnia [OECD TG 202] was greater than 1000 mg/L. Two acute toxicity studies on fish were also conducted. In one study, the LC_{50} was 2730 mg/L (48 hr, Leuciscus idus (L.)) and in another study, the LC_{50} was greater than 100 mg/L [OECD TG 203] (96 hr, Medaka).

In chronic toxicity studies to aquatic species, the NOEC (reproduction) for Daphnia [OECD TG 211] was greater than 100 mg/L . As for chronic toxicity to Green algae, the NOEC (biomass) and NOEC (24-48, 24-72 hr, growth rate) were 556 mg/L and greater than 1000 mg/L, respectively.

A PNEC of 1 mg/L for aquatic organisms was calculated from the lowest NOEC (>100 mg/L) from the 21day Daphnia Reproduction Inhibition test [OECD TG 211] using an assessment factor of 100, because two chronic data (Daphnia and algae) and four acute data (Green algae, Daphnia and fish*)* were available.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work because of its low environmental hazard potential and because it is anticipated based on data presented by the Sponsor country that the exposure to humans is low. However, the substance has properties indicating hazards for human health (developmental toxicity and neurotoxicity) and uncertainty regarding mutagenicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. It is noted that a micronucleus test will be conducted.

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I. Prüfung an der Rattenbauchhaut und subakute perkutane Toxizität
II. Prüfung an der Meerschweinchen – Rückenhaut
III. Prüfung an der Kaninchen – Rückenhaut

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I. Akute perorale Toxizität
II. Subakute perorale Toxizität

BASF AG, unpublished report; summary (14.4.67 b); Gewerbehygienisch – Pharmakologisches Institut; Toxizität für Katzen:
I. Akute perorale Toxizität
II. Subakute perorale Toxizität

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APPENDIX

Recalculation manner for doses mentioned in the study by Aratani (1993)

	Approximate average body weight during exposure period calculated from body weight curve (g)[a)]		**Average water intake during exposure period (ml/day)[b)]**		**Average re-calculated dose/body (mg/day)[c)]**		**Average re-calculated dose (mg/kg/day)[d)]**		**Original dose mentioned in the literature by Aratani (mg/kg/day)**	
dose(concentration)	Rats (Wistar)	Mice (ddY)	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice
control	630	44	14	5.7	0	0	0	0	0	0
200ppm(200mg/L)	605	47	14	5.7	2.8	1.14	4.6	24.3	2.8-1.2	5.1-3.3
400ppm(400mg/L)	613	46	14	5.7	5.6	2.28	9.1	49.6	5.0-2.3	10.6-6.1
800ppm(800mg/L)	574	38	14	5.7	11.2	4.56	19.5	120	9.6-4.6	17.5-9.5
1200ppm(1200mg/L)	531	31	14	5.7	16.8	6.84	31.6	220.6	15.2-7.1	20.2-19.3

a) Approximate average body weights during exposure period were calculated from the weight of paper cut off from figure 1 in the original literature for each dose

b) Following sentences were referred for Average water intake during exposure period. "Until approximately 10weeks after commencement of treatment, food and water intakes per weight were gradually decreased. After this period, food and water intake per weight became stable, and average water intake a day was 14±2 g for rats and 5.7±1.3 g for mice."

c) Average re-calculated dose/body (mg/day) = Test substance concentration in drinking water (mg/L)/1000× Average water intake during exposure period (ml/day)

d) Average re-calculated dose (mg/kg/day) = Average re-calculated dose/body (mg/day) /Approximate average body weight during exposure period calculated from body weight curve (g)×1000

S I D S

D o s s i e r

Existing Chemical	:	ID: 79-39-0
CAS No.	:	79-39-0
EINECS Name	:	Methacrylamide
EC No.	:	201-202-3
TSCA Name	:	2-Propenamide, 2-methyl-
Molecular Formula	:	C4H7NO

Producer related part

Company	:	Mitsui Chemicals, Inc.
Creation date	:	30.01.2001

Substance related part

Company	:	Mitsui Chemicals, Inc.
Creation date	:	30.01.2001

Printing date	:	25.02.2003
Revision date	:	
Date of last update	:	09.01.2003
Number of pages	:	91
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organisation
Name : Mitsui Chemicals, Inc.
Contact person : Katsuhiko Inaba
Street : 1144, Togo, Mobara-shi
Town : Chiba-ken 297-0017
Country : Japan
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Telefax : +81-475-23-8440
Email : Katsuhiko.inaba@mitsui-chem.co.jp
Homepage :
Source : Mitsui Chemicals, Inc.
30.04.2002

Type : cooperating company
Name : Rohm and Haas European Operations
Contact person :
Street : Lenning House, 2 Masons Avenue
Town : CR9 3NB London
Country : United Kingdom
Phone : +44 686 8844
Telefax : +44 667 9677
Telex : 917266
Remark : Contact Point: Dr. M.F. Wooder
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

Type : cooperating company
Name : Röhm GmbH & Co. KG
Contact person :
Street : Kirschenallee
Town : 64293 Darmstadt
Country : Germany
Phone : + 49 6151 18 4241
Telefax : + 49 6151 18 3213
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Dr. H. Müllerschön, Dep. U-PTT, phone: +49 6151 184241
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Dipl.-Ing. G. Ritz, Dep. U-PTT, phone: +49 6151 183005
Source : Röhm GmbH & Co. KG Darmstadt
19.04.2002

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : Manufacturer
Name of plant : Mitsui Chemicals, Inc. Mobara Center
Street : 1900, Togo, Mobara-shi
Town : Chiba-ken 297-0017
Country : Japan
Source : Mitsui Chemicals, Inc.
29.04.2002

1.0.3 IDENTITY OF RECIPIENTS

Name of recipient	:	Mr.Koji Tomita, Ministry of Foreign Affairs, Economic Affairs Bureau, Second International Organisation Div.
Street	:	2-2-1 Kasumigaseki, Chiyoda-ku
Town	:	Tokyo 100-6070
Country	:	Japan
Phone	:	+81-3-3581-0018
Telefax	:	+81-3-3581-9470
Email	:	
Homepage	:	
Source	:	Mitsui Chemicals, Inc.

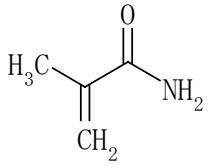
28.04.2002

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	2-methyl-2-propenamide
Molecular formula	:	C_4H_7NO
Molecular weight	:	85.11
Source	:	Mitsui Chemicals, Inc.

Structure



30.04.2002

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	Organic
Physical status	:	Solid
Purity	:	>= 99 % w/w
Colour	:	White
Odour	:	Odourless
Source	:	Mitsui Chemicals, Inc.

28.04.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2-Methacrylamide

Source	:	Mitsui Chemicals, Inc.

Röhm GmbH & Co. KG Darmstadt
03.06.1997

2-Methyl-2-propenamide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

2-Methylacrylamide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

2-Methylpropenamide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
01.02.2002

2-Propenamide, 2-methyl- (9CI)
Source : Mitsui Chemicals, Inc.
27.03.2002

Alpha-methyl acrylic amide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

Methacrylamide (8CI)
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

Methacrylic acid amide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

Methacrylic amide
Source : Mitsui Chemicals, Inc.
Röhm GmbH & Co. KG Darmstadt
03.06.1997

Methylacrylamide
Source : Mitsui Chemicals, Inc.
28.04.2002

Prop-2-enamide, 2-methyl- (PICCS)
Source : Mitsui Chemicals, Inc.
01.02.2002

1.3 IMPURITIES

Purity : Typical for marketed substance
CAS-No : 5536-61-8
EC-No : 226-896-5
EINECS-Name : Sodium methacrylate
Molecular formula : $C_4H_6O_2.Na$

Value :
Source : Mitsui Chemicals, Inc.
19.04.2002 (62)

Purity : Typical for marketed substance
CAS-No : 7783-20-2
EC-No : 231-984-1
EINECS-Name : ammonium sulphate
Molecular formula : $H_3N.1/2H_2O_4S$
Value :
Source : Mitsui Chemicals, Inc.
19.04.2002 (62)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 8500 tonnes in 2001 as the capacity for production (worldwide)
Source :
30.04.2002

1.6.1 LABELLING

Labelling : provisionally by manufacturer/importer
Specific limits : No
Symbols : Xn
Nota : D
R-Phrases : (20/22) Harmful by inhalation and if swallowed
S-Phrases : (22) Do not breathe dust
(24) Avoid contact with skin
Remark : Roehm GmbH
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

1.6.2 CLASSIFICATION

Classified : provisionally by manufacturer/importer
Class of danger : Harmful
R-Phrases : (20/22) Harmful by inhalation and if swallowed
Specific limits :
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

Industry category : 11 Polymers industry
Use category : 2 Adhesive, binding agents
Extra details on use category : Polymer processing
No extra details necessary
Emission scenario document : not available
Source : Mitsui Chemicals, Inc.
28.04.2002 (65)

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value :
Remark : MAK-value does not exist.
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (25)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation :
Substance listed : No
No. In Seveso directive :
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : 3.1.7 (organic substances)
Class of danger : I
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information : EINECS No. 201-202-3
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : DSL
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : AICS
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : ENCS
Additional information : ENCS No. 2-1065
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : ECL
Additional information : ECL Serial No. KE-24899
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : PICCS
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : Poisonous Chemicals List (Switzerland)
Additional information : Giftliste 1 (List of Toxic Substances 1)
Toxic Category 2: Acute Oral lethal dose of 5 - 50mg/kg
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

Type : other: WHMIS Ingredint List (Canada)
Source : STN FILE CHEMLIST (20020322/UP)
19.04.2002

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Source of exposure : Residual monomer content
Exposure to the : Substance
Remark : Residual monomer content of polymers is ca. 0.5% or less.
Source : Mitsui Chemicals, Inc.
19.04.2002 (64)

Source of exposure : Measurement at workingplace
Exposure to the : Substance
Remark : On Oct. 1990 exposure level of methacrylamide was measured at Packing place. Absorbed substance was analyzed by GC.
Sampling method
–sampling method; water
–sampling instrument; inpinjar
–absorbed rate; 15L/min
–absorbed volume; 900L
–sampling time; for 60 minutes
–number of replicate; 5 times in a day
Result : Monitoring data : 0.07 – 0.56 mg/m^3
Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
29.04.2002 (57)

Source of exposure : Measurement at workingplace
Exposure to the : Substance
Remark : On July 2002 exposure level of methacrylamide was measured at Working place. Absorbed substance was analyzed by HPLC.
Sampling method
–sampling method; 2% acetnitril/phosphate buffer (pH4)
–sampling instrument; inpinjar
–absorbed rate; 1L/min
–absorbed volume; 30L
–sampling time; for 30 minutes
–number of replicate; 6 or 3 times in a day
Result : Monitoring data: Sampling for process evaluation; 0.79 – 0.93 mg/m^3
Analysis for process evaluation; 0.07 – 0.18 mg/m^3
Sampling for product evaluation; 0.13 – 0.16 mg/m^3
Monitoring of packing process; 0.06 – 0.18 mg/m^3
Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
10.07.2002 (58)

Remark : Emissions during production
Methacrylamide is produced in closed systems and hence emissions during production are extremely low. Normally no release into sewage water systems occurs (well below 1 t/year).
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (94)

Remark : Residual monomer content
Residual monomer content of polymers is usually very low (below 0.1 %). Typical residual monomer contents are 0.001 % to 0.01 %.
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (98)

Remark : Migration
Migration of residual unpolymerised methacrylamide from polymer articles

is very low, as typified migration into food simulant under EEC food regulations for plastic materials (Directive 90/128/EEC).
Experiments conditions for food contact approval in Directive 90/128/EEC.
–Deionised water, 10 days at 40 degree C and 2 hours at 70 degree C
–3% acetic acid, 10 days at 40 degree C and 2 hours at 70 degree C
–15% ethanol, 10 days at 40 degree C and 2 hours at 70 degree C
–Isooctane, 2 days at 20 degree C and 0.5 hours at 40 degree C
(isooctane is used as replacement for vegetable oil for analytical reasons)

Result : Migration of residual methacrylamide from plastic materials for food contact is very low under these conditions. The Specific Migration Limit (SML) is below 0.02 mg/kg (that means below 0.02 mg methacrylamide in 1kg food simulant).

Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.

10.07.2002 (2) (80)

Remark : Between 01.03.1990 and 17.09.1197 24 work place exposure measurements of methacrylamide were done. All measurements were done by personal-air sampling. Adsorption has been carried out by silica gel or activated carbon or the substance was filtered by paper filter or glass fiber
filter. Adsorbed substance was desorbed with phosphoric acid, water or carbon disulfide and analyzed by HPLC or gas chromatography.
Workplace measurements during packaging, production of monomers or production of solvent polymers and delivery of methacrylamide.

Result : 3 short term measurements (30 minutes): 0,16 to 0,25 mg/m^3
21 long term measurements (3,5 - 7,5 h): 0, 01 to 2, 10 mg/m^3

Source : Röhm GmbH & Co. KG Darmstadt

Reliability : (2) valid with restrictions

28.04.2002 (95) (96) (97) (99) (100) (101) (102)

1.11 ADDITIONAL REMARKS

Memo : Disposal of waste
Remark : Waste of the production process are incinerated.
Source : Mitsui Chemicals, Inc.
30.04.2002 (60)

Memo : Disposal of waste
Remark : Methacrylamide must be disposed of as a special waste in accordance with the regulations for special waste.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 111.3 °C
Sublimation	:	Ambiguous
Method	:	other: no data
Year	:	2001
GLP	:	no data
Test substance	:	other TS
Source	:	METI Japan
Test substance	:	WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

29.04.2002 (48)

Value	:	= 106 - 112 °C
Sublimation	:	Yes
Method	:	other: no data
Year	:	1996
GLP	:	no data
Test substance	:	
Remark	:	Sublimation temperature: 95 – 105 degree C
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions

03.06.1997 (88)

Value	:	= 109 - 111 °C
Sublimation	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	other TS
Source	:	Röhm GmbH & Co. KG Darmstadt
Test substance	:	Purity: 98% Impurities: water < 2%
Reliability	:	(2) valid with restrictions Secondary Literature, handbook data.

22.04.2002 (1)

Value	:	= 110 - 111 °C
Sublimation	:	
Method	:	other: no data
Year	:	1992
GLP	:	no data
Test substance	:	
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Secondary literature, handbook data.

03.06.1997 (18) (117)

Value	:	= 110 °C
Sublimation	:	
Method	:	other: no data
Year	:	1976
GLP	:	no data
Test substance	:	
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Secondary literature, handbook data.

03.06.1997 (16) (39) (115)

2.2 BOILING POINT

Value : = 225 °C at 1013 hPa
Decomposition :
Method : other: JIS K2233-1984
Year : 2001
GLP : no data
Test substance : other TS
Source : METI Japan
Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.04.2002 (48)

Value : ca. 215 °C at 1013 hPa
Decomposition : Yes
Method : other: no data
Year : 1996
GLP : no data
Test substance :
Remark : Sublimation temperature: 95 – 105 degree C
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

2.3 DENSITY

Type : Density
Value : = 1.138 g/cm³ at 25 °C
Method : other: JIS K7112-1980
Year : 2001
GLP : no data
Test substance : other TS
Source : METI Japan
Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (2) valid with restrictions
29.04.2002 (48)

Type : Density
Value : 1.1 - 1.12 g/cm³ at 20 °C
Method : other: no data
Year : 1996
GLP : no data
Test substance :
Remark : Form: crystalls
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

Type : bulk density
Value : = 550 kg/m^3 at 20 °C
Method : other: no data
Year : 1993
GLP : no data

Test substance :
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

Type : Density
Value : = 1.1 g/cm³ at °C
Method : other: no data
Year : 1976
GLP : no data
Test substance :
Remark : Temperature: no data
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (39)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .00013 hPa at 25 °C
Decomposition : No
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2001
GLP : No
Test substance : other TS
Source : METI Japan
Test condition : Test Temperature: 60, 70, 80 degree C
Number of replicate: n=3
Flow rate: 20 - 40 mL/min
Solvent for absorption: pure water
Carrier gas: extra pure N2 (99.99%)
Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.04.2002 (48)

Value : = .14 hPa at 20 °C
Decomposition :
Method : other (calculated): according to Haas & Newton
Year : 1976
GLP : No
Test substance :
Remark : Base of calculation: Boiling point: 215 degree C (at 1013 hPa)
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (31)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = -.15 at 25 °C
pH value : = 6.2 6.3
Method : OECD Guide-line 107 "Partition Coefficient (1-octanol/water), Flask-shaking Method"
Year : 2000

GLP : Yes
Test substance : other TS
Result : LOG POW

Test	A	B	Average
No.1	-0.13 (6.3)	-0.15 (6.2)	
No.2	-0.17 (6.2)	-0.17 (6.2)	-0.15
No.3	-0.13 (6.2)	-0.13 (6.2)	

() is pH of water layer

Source : MITI Japan
Test condition : SAMPLE WEIGHT: 5.05 mg
COMPONENT OF TEST SOLUTION:

Case	No.1	No.2	No.3
1-octanol saturated by water	5mL	10mL	20mL
water saturated by 1-octanol	30mL	25mL	15mL

TEMPERATURE: 24 - 26 degree C
REVOLUTION: 20/min x 5 min
NUMBER OF REPLICATE: 2
ANALYSIS: HPLC

Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
01.03.2002 (56)

Partition coefficient :
Log pow : = -.51
pH value :
Method : other (calculated): according to Rekker
Year : 1977
GLP : No
Test substance :
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Accepted calculation method according to Rekker (1977).
31.08.1998 (75) (88)

Partition coefficient :
Log pow : = -.23 at °C
pH value :
Method : other (measured)
Year : 1984
GLP : no data
Test substance :
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.
18.01.2001 (108)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	>= 100 g/L at 25 °C
Method	:	OECD Guide-line 105
Year	:	2001
GLP	:	no data
Test substance	:	other TS
Source	:	METI Japan
Test substance	:	WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

29.04.2002 (48)

Solubility in	:	
Value	:	= 202 g/L at 20 °C
pH value	:	= 7.1
concentration	:	100 g/L at 20 °C
Description	:	Miscible
Method	:	other: no data
Year	:	1996
GLP	:	no data
Test substance	:	
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (88)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result	:	no data
Method	:	other: calculated according to Shebeko (1983)
Year	:	
GLP	:	
Test substance	:	
Method	:	Values assume 298 K and 1 atmosphere. Higher temperatures and/or higher pressures will lower the lower limit and raise the upper limit.
Remark	:	Explosion limits: lower value: 2.0 vol.% in air upper value: 15.1 vol.% in air
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Accepted calculation method.

03.06.1997 (104)

Result : no data
Method : other:
Year : 1997
GLP : no
Test substance : As prescribed by 1.1 - 1.4
Method : Explosive concentration of dust in air: Hartman type (1-liter volume)
Result : Minimum explosive concentration: 55mg/L in air
Limiting oxygen concentration: 12% (Sample concentration; 825mg/L)
Minimum ignition energy: 75mJ (Sample concentration; 825mg/L)
Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
09.01.2003 (67)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : Dissociation not being occurred
Method : OECD Guide-line 112
Year : 2001
GLP : No
Test substance : Other TS
Source : METI Japan
Test condition : TITRATION METHOD
–concentration of test substance; 800 mg/L (9.40 mmol/L)
–standard solution; 0.1 mol/L NaOH (f=1.001)
0.1 mol/L HCl (f=1.000)
–number of replicate; 1

SPECTROPHOTOMETRIC METHOD
–concentration of test substance; 800 mg/L (9.40 mmol/L)
80 mg/L (0.94 mmol/L)
-cell constant; 0.963cm^{-1}
–number of replicate; 5
Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (1) valid without restriction
29.04.2002 (48)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Colour
Remark : Colourless
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

Memo : Conversion factor

Remark : Value: 1 ppm = 3.48 mg/m^3
1 mg/m^3 = 0.29 ppm (at 1013 Pa; Temp.: 25 deg. C)
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

Memo : Corrosion
Remark : The inhibitive action on corrosion of mild steel in sea water by Methacrylamide has been investigated using galvanostatic polarization measurements at 35, 45, and 55 °C. The additive retard the dissolution reaction, the extent of which depends on the concentration of Methacrylamide and the temperature. The corrosion rate of mild steel in sea water was decreased upto 65 % by Methacrylamide (concentration: 1 M) at 35 °C.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.
03.06.1997 (37)

Memo : Disposal considerations
Remark : Waste is hazardous and therefore particularly to be kept under surveillance. It must be disposed of in accordance with the regulations after consultation of the competent local authorities and the disposal company in a suitable and licensed facility.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

Memo : Henry's law constant
Remark : Value (calculated): 5.899 10E-3 Pa*m^3/mol at 25 degree C
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (42)

Memo : Odour
Remark : Odourless
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (88)

Memo : Saturation concentrations
Remark : Saturation concentations of Methacrylamide in the gasphase at various temperatures:

Temperature [degree C]	Saturation concentration [mg/m^3]
25	< 23
30	ca. 16
40	97
50	301
80	3580

Method: GC
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (86)

Memo : Storage
Remark : The storage temperature should not exceed 30 degree C. With peroxides and incident light polymerization may occur. Therefore contamination should be avoided. Shelflife of unstabilizied monomer is 3 month.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (79)

Memo : Vaporization rate
Remark : Vaporization rate of methacrylamide in low vacuum (1*10E-3 Torr):
Methacrylamide: 2.5 mg/hour (at 25 degree C)
30.0 mg/hour (at 40 degree C)
The weight of the monomer before exposure to vacuum was approximately 100 mg.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (38)

3.1.1 PHOTODEGRADATION

Type	:	Air
Light source	:	Sun light
Method	:	other (calculated): SRC AOP Ver.1.90 (USEPA)
Year	:	2000
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	INDIRECT PHOTOLYSIS –Sensitizer: OH –Concentration of sensitizer: $1.5X10^{6}$ hydroxyl radical/cm^3 --Rate constant: $2.0X10^{-13}$ cm^3/molecule-sec –Degradation: half-life is 0.5 day
Source	:	Mitsui Chemicals, Inc.
Flag	:	Critical study for SIDS endpoint

11.06.2002 (63)

Type	:	Air
Light source	:	Sun light
Method	:	other (calculated): SRC AOP Ver.1.90 (USEPA)
Year	:	2000
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	INDIRECT PHOTOLYSIS–Sensitizer: OZONE –Concentration of sensitizer: $7.0X10^{11}$ molecule/cm^3 --Rate constant: $1.1X10^{-17}$ cm^3/molecule-sec --Degradation: half-life is 1.0 day
Source	:	Mitsui Chemicals, Inc.
Flag	:	Critical study for SIDS endpoint

11.06.2002 (63)

3.1.2 STABILITY IN WATER

Type	:	Abiotic
t1/2 pH4	:	> 5 day(s) at 50 °C
t1/2 pH7	:	> 5 day(s) at 50 °C
t1/2 pH9	:	> 5 day(s) at 50 °C
Deg. product	:	No
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2001
GLP	:	No
Test substance	:	other TS
Result	:	Stable at pH4, 7 and 9 ($t_{1/2}$ > 5days at 50 degree C)
Source	:	METI Japan
Test condition	:	Concentration of test substance: 50 mg/L Temperature: 49 - 51 degree C Vessel: flask with a plug Number of replicate: 2 Period: 5 days
Test substance	:	WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

30.04.2002 (48)

Type	:	abiotic
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"

Year : 1995
GLP : No
Test substance :
Remark : Under the test conditions discribed according to OECD 111 (Temp.: max. 40 °C) hydrolysis of Methacrylamide is not significant at pH 4, 7, and 9.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Guideline study, no GLP
28.04.2002 (87)

3.1.3 STABILITY IN SOIL

Remark : Degradation by soil microorganisms is expected when methacrylamide is released to the soil.
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (40) (70) (116) (119)

3.2.1 MONITORING DATA

Type of measurement : Background concentration
Media : surface water
Concentration :
Method : Analysed by HPLC
--Eluent: 2% acetnitril/phospate buffer
--Column: Finepack SIL-C18-5 4.6X250
--Gurd Column: Finepack SIL-C18T-5P 4.6X50
–Temperature: 40 degree C
--Flow rate: 0.9 mL/min
–Wave length: UV210 nm
–Injection volume: 5 uL
Result : Monitoring Concentrations

Sampling site	Conc.(mg/L) 01.July 2002	08.July.2002
River water		
ca.50m upstream from the outfall	-	<0.1
ca.50m downstream from the outfall	0.8	<0.1
ca.400m downstream from the outfall	0.3	<0.1
ca.5000m downstream from the outfall	-	<0.1
effluent of sewage treatment plant	0.3	0.2
waste water line1	12	-
waste water line2	2100	-

-: not available
Limit of detection = 0.1 mg/L
Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
12.07.2002 (59)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : Adsorption
Media : other: soil – water
Method : other: calulation
Year : 1982
Remark : The soil adsorption coefficient can be calculated from the log Pow (-0.51) using the following equation: logKoc = 0.544 * logPow + 1.377
Koc = 12.6 Soil adsorption is therefore considered to be low.
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (41)

Type : Volatility
Media : water – air
Method : Other
Year :
Remark : As Henry's law constant is well below 3*10 E-2 Pa*m^3/mol volatization from water into air is considered negligible.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997

Type :
Media : water – air
Method : other: Determination of concentration in water and air
Year : 1978
Remark : Equilibrium concentrations between water and air were determined at the boiling point of the solutions. The majority the substance remained in the water phase (96.5 - 98.2 %).
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (45)

3.3.2 DISTRIBUTION

Media : air - biota – sediment(s) - soil – water
Method : Calculation according to Mackay, Level III
Year : 2002
Result : Table Environmental distribution of Methacrylamide using the Fugacity model (Level III)

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0%	0.0%	0.0%
Water	41.9%	99.6%	33.5%
Soil	58.0%	0.0%	66.4%
Sediment	0.2%	0.4%	0.1%

Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
22.04.2002 (61)

Media : air – biota sediment(s) soil – water
Method : Calculation according Mackay, Level I
Year : 1992

Remark : Compartment %

Air	0.20
Water	99.79
Soil	0.00
Sediment	0.00
Suspended matter, aquatic	0.00
Biota	0.00

Compound properties:
Molecular weight: 85.1 g/mol
Aqueous solubility: 2.020 10E+5 g/m^3
Vapour pressure: 1.4 10 E+1 Pa
Henry's constant: 5.899 Pa*m^3/mol
Log Pow : - 0.51
Temperature: 25 degree C

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Accepted calculation method according to Mackay (1992).
28.04.2002 (42)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : Aerobic
Inoculum : activated sludge, non-adapted
Concentration : 100 mg/L related to Test substance (OECD Guide-line 301C)
30 mg/L related to Test substance (OECD Guide-line 302C)
Contact time : 28 day(s)
Degradation :
Result : inherently biodegradable
Control substance : Aniline
Kinetic of cont. Subst. : 7 day(s) = 61 %
14 day(s) = 74 %
Deg. product : -
Method : OECD Guide-line 301C "Ready Biodegradability: Modified MITI Test (I)" and OECD Guide-line 302C "Inherent Biodegradability: Modified MITI Test (II)"
Year : 1997
GLP : Yes
Test substance : other TS
Method : <Original test>
-Method; OECD Guide-line 301C "Ready Biodegradability: Modified MITI TEST (I)"
–Contact time; 28days
–Concentration; 100 mg/L related to Test substance
<Suplemental test>
-Method; OECD Guide-line 302C "Inherent Biodegradability: Modified MITI TEST (II)"
Contact time; 28days
–Concentration; 30 mg/L related to Test substance
Result : <Original test>
-Degradation; 24% (BOD), 32% (TOC), 31% (HPLC)
<Suplemental test>

-Degradation; 95% (TOC), 100% (HPLC)
–Results; inherently biodegradable

Source : MITI Japan
Test substance : WAKO Pure Chemicals Industries, Ltd. (Lot. PAL0299) Purity; 99.3%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.04.2002 (55)

Type : Aerobic
Inoculum : activated sludge
Concentration : 100 mg/L related to DOC (Dissolved Organic Carbon)
Contact time :
Degradation : 97 % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 1 day(s) = 3 - 5 %
3 day(s) = 14 - 16 %
10 day(s) = 78 - 96 %
13 day(s) = 96 %
21 day(s) = 98 - 99 %
Deg. product :
Method : OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year : 1988
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Purity: 99.4 %; unstabilized
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Guideline study, screening test, no GLP.
Flag : Critical study for SIDS endpoint
09.01.2003 (81)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other: caluculated according to Lyman
BCF : = .45
Method :
Year : 2002
GLP : no
Test substance :
Remark : The bioaccumulation potential is predicted from the 1-Octanol/water partition coefficient (logPOW = -0.15) using the equation:
log BCF = 0.76 X logPOW - 0.23
From the derived BCF no bioaccumulation of substance is predicted.
Source : Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.04.2002 (41) (56)

BCF : = .24
Method : other: calculated according to Lyman
Year : 1982
GLP : no

Test substance :
Remark : The bioaccumulation potential is predicted from the 1-octanol/water partition coefficient (logPow: -0.51) using the equation:
log BCF = 0.76 * logPow 0.23
From the derived BCF no bioaccumulation of the substance is predicted.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Accepted calculation method according to Lyman et al. (1982).

28.04.2002 (41)

3.8 ADDITIONAL REMARKS

Memo : Aliphatic amide degradation
Remark : Strains of Pseudomonas sp. (soil bacterium) and Xanthomonas maltophila capable of utilizing acrylamide as sole C- and N-source were tested for their ability to degrade a mixture of acrylamide, propionamide, butyramide and methacrylamide.
Batch cultures of Pseudomonas sp. degraded 5.6 mM Methacrylamide to 0.6 mM in 72 hours. Methacrylamide was transformed to acrylic acid, methacrylic acid and ammonia with a degradation rate of 78 umol/L.
Batch cultures of Xanthomonas maltophila degraded the mixture in 48 hours. Faster degradation rates (2 hours at the rate of 2800 umol/h for Pseudomonas sp.) were obtained when the strains were immobilizied in calcium alginate.
Both strains produced stoichiometric amounts of corresponding carboxylic acids and ammonia.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

03.06.1997 (69) (71) (103)

Memo : Aliphatic amide degradation
Remark : A Pseudomonas putida isolate capable of utilizing
Methacrylamide as sole C- and N-source was immobilized in calcium alginate beads. When Methacrylamide was used as substrate (temperature: 25 °C, test concentration: 1000 ppm), the initial pH of the medium (pH: 6.7) increased rapidly and then remained constant after 96 - 120 hours. The
final pH was 7.2. Mass balances indicated that approximately 85 % of C and N was recovered in the form of CO_2 and NH_3 during the degradation of Methacrylamide.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

03.06.1997 (21)

Memo : Aliphatic amide degradation
Remark : A mixed microbial culture was isolated from an environment contaminated with organic cyanides and polychlorinated biphenyls (PCB's). This mixed culture could utilize Methacrylamide as the sole source of carbon and nitrogen.
The mixed microbial culture was grown for 48 hours on the phosphate buffer medium (pH 7.0) containing Methacrylamide (1 g/L) as the sole source of carbon and nitrogen at 30 °C. The protein concentration of the inoculum was 0.085 mg/L. The final protein concentration was 7.62 mg/L,

ammonia 51.6 umol/ml and pH 8.31, respectively.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

03.06.1997 (20)

Memo : Enzyme formation
Remark : A strain of nitrile hydratase-forming microorganism, Corynebacterium pseudodiphteriticum ZBB-41, was isolated from soil and the conditions for the enzyme formation have been studied. The addition of Methacrylamide (0.5 % w/v) as an inducer greately enhanced enzyme formation.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

03.06.1997 (118)

Memo : Hydrolysis
Remark : The acid-catalyzed hydrolysis of amides is a two-step process, in which a pre-equilibrium protonation step is followed by a nucleophilic attack of a water molecule on the protonated species, which leads to the products.

Step 1: A (amide) + H^+ = AH^+
Step 2: AH^+ + H_2O ----> Carboxylic acid + NH_4^+

The rates of hydrolysis of Methacrylamide in sulphuric acid up to 46 % have been measured over the temperature range of 65 to 85 °C. A rate maximum was observed between 31 and 27 % acid, depending on the temperature.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

22.04.2002 (43)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/L
LC0 : > 100 measured/nominal
LC50 : > 100 measured/nominal
LC100 : > 100 measured/nominal
Limit test : Yes
Analytical monitoring : Yes
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 2000
GLP : Yes
Test substance : other TS
Result : Table 1 NOMINAL/MEASURED CONCENTRATION:

Nominal conc (mg/L)	Measured conc. (mg/L) (% of nominal) 0hr*	24hr**	mean
Control	<0.5	<0.5	
100mg/L	90.5 (90.5)	94.4 (94.4)	92.4

* ; freshly prepared test solution
**; test solution after 24hr exposure period

TEST TEMPERATURE: 23.1 – 23.8 degree C
pH: 6.9 – 7.0
DISSOLVED OXYGEN: 6.4 – 11.3 mg/L

EFFECT OF MORTALITY: none at Control and 100 mg/L
SYMPTOMS: none of abnormalities at Control and 100 mg/L
STATISTIC: no data

Source : EA Japan
Test condition : Test Organism:
–supplier; Aichi Yatomi chiku fish farm (Aichi, Japan)
–size/weight; 21.2 mm (18.7 - 22.9 mm), n=10/0.1392 g (0.0913 - 0.1855 g),
n=10
–feeding during acclimation; "TETRAMIN"
–acclimation; acclimated to dilution water for more than 12 days before testing
–feeding during test; none, feeding was stoped before 24hr of the test
STOCK AND TEST SOLUTION AND THEIR PREPARATION:
--solvent; no solvent was used
--stock of solution; no data
REFERENCE SUBSTANCE: $CuSO_4$-$5H_2O$ LC_{50} (96hrs) = 0.59 mg/L
DILUTION WATER:
--source; dechlorinated tap water
–aeration; no data
–hardness; 41.0 mg/L as $CaCO_3$
pH; 6.8
TEST SYSTEM
–concentration; 0, 100 mg/L
–detail test method; semi-static
–renewal of test solution; 24hr

–exposure vessel type; 3L glass vessel
–number of replicates/fish per replicate; 1/10
–test temperature; 23 - 25 degree C
–intensity of irradiation; room light
–photoperiod; 16hr - 8hr light-dark cycle
DURATION OF THE TEST: 96hr
TEST PARAMETER: mortality, abnormal behavior and abnormal respiration
SAMPLING: at 0 and 24hr
MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by GC

Test substance : KISHIDA CHEMICALS CO., LTD (Lot No. D12358J) purity >= 98%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.04.2002 (29)

Type : Static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/L
LC0 : = 933
LC50 : = 2730
LC100 : = 7989
Analytical monitoring : no data
Method : other: Acute toxicity for fish, DIN 38412 Teil 15
Year : 1987
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions, GLP.
Flag : Critical study for SIDS endpoint
22.04.2002 (91)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/L
NOEC : > 1000 measured/nominal
EC0 : > 1000 measured/nominal
EC50 : > 1000 measured/nominal
EC100 : > 1000 measured/nominal
Limit Test : Yes
Analytical monitoring : Yes
Method : OECD Guide-line 202
Year : 2000
GLP : Yes
Test substance : other TS
Result : Table NOMINAL/MEASURED CONCENTRATION

Nominal conc. (mg/L)	Measured conc. (mg/L) (% of nominal)		
	0hr*	48hr**	mean

		Control <0.5 <0.5 1000mg/L 984.7 (98.5) 892.6 (89.3) 937.5 --- * ; freshly prepared test solution **; test solution after 48hr exposure period TEST TEMPERATURE: 19.9 – 20.6 degree C pH: 7.4 – 7.5 DISSOLVED OXYGEN: 8.4 - 8.9 mg/L EFFECT DATA (IMMOBILIZATION) 24hr EiC_{50} > 1000 mg/L 48hr EiC_{50} > 1000 mg/L 48hr NOEiC > 1000 mg/L MORTALITY OR IMMOBILITY No mortality and immobility at Control and 1000 mg/L of 2-Methyl-2-propenamide. STATISTICS: no data
Source	:	EA Japan
Test condition	:	Test Organism: -supplier; National Institute of Environmental Studies (Japan) -age; juvenile Daphnia magna less than 24hr old –feeding during acclimation; *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual –acclimation; 21 days –feeding during test; none STOCK AND TEST SOLUTION AND THEIR PREPARATION: -solvent; no solvent was used -stock of solution; no data REFERENCE SUBSTANCE: $K_2Cr_2O_7$ EiC_{50} (48hrs) = 0.60 mg/L DILUTION WATER: -source; M4 medium (refer to OECD-TG 211) –hardness; 249 mg/L as $CaCO_3$ –pH; 8.3 TEST SYSTEM –concentration; 0, 1000 mg/L –renewal of test solution; none –exposure vessel type; 100 mL test solution in a 100 mL glass vessel –number of replicates/individual per replicate; 4/5 –test temperature; 19 - 21 degree C –intensity of irradiation; room light –photoperiod; 16hr - 8hr light-dark cycle DURATION OF THE TEST: 48hr TEST PARAMETER: immobility SAMPLING: at start and end of test MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by GC
Test substance	:	KISHIDA CHEMICALS CO., LTD (Lot No. D12358J) purity >= 98%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.04.2002 (26)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)

Unit : mg/L
NOEC : = 556 measured/nominal
EC50 : > 1000 measured/nominal
Limit test : Yes
Analytical monitoring : Yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2000
GLP : Yes
Test substance : other TS

Result : Table 1 NOMINAL/MEASURED CONCENTRATION

Nominal conc. (mg/L)	Measured conc. (% of nominal) 0hr*	72hr**
<Original Test>		
Control	<0.5	<0.5
1000mg/L	1011 (101.1)	926 (92.6)
<Supplemental test>		
Control	<0.5	<0.5
556mg/L	599 (107.7)	556 (100.0)

* ;initial **;final

TEST TEMPERATURE:
-original test; 21.8 – 22.8 (mean 22.5) degree C
–supplemental test; 21.2 – 23.0 (mean 22.5) degree C
pH:
-original test; 7.0 - 7.3 at start, 8.1-8.6 at end of test
–supplemental test; 7.3 – 7.5 at start, 8.9 - 9.0 at end of test

EFFECT DATA/ELEMENT VALUES:
-area method; EbC_{50} (0 - 72hr) > 1000 mg/L
NOEbC (0 - 72hr) = 556 mg/L
-rate method; ErC_{50} (24 - 48hr) > 1000 mg/L
NOErC (24 - 48hr) = 1000 mg/L
ErC_{50} (24 - 72hr) > 1000 mg/L
NOErC (24 - 72hr) = 1000 mg/L

Table 2 AVERAGE CELL DENSITY OF *Selenastrum capricornutum*

Nominal conc. (mg/L)	Cell Density (1x10E+4 cell/mL) 0hr	24hr	48hr	72hr
<Original Test>				
Control	1.0	5.5	34.7	201.6
1000mg/L	1.0	5.0	30.6	197.3
<Supplemental test>				
Control	1.0	5.2	33.5	204.4
556mg/L	1.0	5.3	40.6	212.2

Table 3 AVERAGE GROWTH INHIBITION

Nominal conc. (mg/L)	Inhibition area method (0-72hr)%	growth rate (24-48hr)%	growth rate (24-72hr)%

<Original Test>
Control - - -
1000mg/L 4.82 1.59 -2.08
<Supplemental test>
Control - - -
556mg/L -7.99 -9.36 -0.34

STATISTICS: F&t-test; Yukms StatLight #3 “Pairwise Comparisons“

Source : EA Japan

Test condition : Test Organism:
-strain; ATCC-22662
–supplier; American Type Culture Collection
–acclimation; 3 days
–initial cell concentration; 1X10E+4 cells/mL
STOCK AND TEST SOLUTION AND THEIR PREPARATION:
-solvent; no solvent was used
-stock of solution; no data
REFERENCE SUBSTANCE: $K_2Cr_2O_7$ EbC_{50} (72hrs) = 0.52 mg/L
TEST MEDIUM CHEMISTRY: OECD medium
TEST SYSTEM
–concentration; 0, 1000 mg/L (original test)
0, 556 mg/L (supplemental test)
–exposure vessel type; 100 mL medium in a 300 mL Erlenmeyer flask with a porous plug
–number of replicates; 3
–test temperature; 21 - 25 degree C
–pH; no adjustment during exposure period
–intensity of irradiation; 4,000 - 5,000 lux
–photoperiod; continuous
–shaking; 100 rpm
TEST PARAMETER: cell concentration (cells/mL)
SAMPLING: at 0, 24, 48 and 72hr
MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by GC

Test substance : KISHIDA CHEMICALS CO., LTD (Lot No. D12358J) purity >= 98%

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

29.04.2002 (28)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : other: bacteria

Species : Pseudomonas putida (Bacteria)

Exposure period : 16 hour(s)

Unit : mg/L

EC10 : > 10000

Analytical monitoring : no data

Method : other: according to Bringmann and Kuehn, DIN 38412 Teil 8

Year : 1988

GLP : No

Test substance : as prescribed by 1.1 - 1.4

Remark : The turbidity of the solution was increased by the degradation products. Inhibition between 20000 and 40000 mg/L.

Source : Röhm GmbH & Co. KG Darmstadt

Reliability : (2) valid with restrictions
Test procedure in accordance with international standard methods with acceptable restrictions.

22.04.2002 (84)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 21 day(s)
Unit : mg/L
NOEC : > 100 measured/nominal
LCEC : > 100 measured/nominal
EC50 : > 100 measured/nominal
LC50 : > 100 measured/nominal
Analytical monitoring : Yes
Method : OECD Guide-line 211
Year : 2000
GLP : Yes
Test substance : other TS
Result : Table 1 NOMINAL/MEASURED CONCENTRATION:

Nominal conc.	Measured conc. (mg/L) 0day *	2day **	6day *	8day **	15day *	17day **	Time weighted mean
Control	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
100.0mg/L	92.5	91.3	99.5	93.6	104.1	100.2	96.9
% of nominal	92.5	91.3	99.5	93.6	104.1	100.2	96.9

* ; freshly prepared test solution
**; test solution after 48hr exposure period

TEST TEMPERATURE: 19.7 – 20.6 degree C
pH: 7.5 – 8.0
DISSOLVED OXYGEN: 8.0 - 9.1 mg/L
HARDNESS: 245 – 254 mg/L as $CaCO_3$

EFFECT DATA (PARENTS)
21day LC_{50} > 100.0 mg/L
EFFECT DATA (REPRODUCTION)
21day EC_{50} > 100.0 mg/L
21day NOEC > 100.0 mg/L
21day LOEC > 100.0 mg/L

Table 2 CUMULATIVE NUMBERS OF DEAD PARENTAL DAPHNIA AND MORTALITY AFTER EXPOSURE OF 21DAY

Nominal Conc.	Number of dead	Mortality (%)
Control	1	10
100.0mg/L	2	20

Table 3 TIME (day) TO FIRST BROOD PRODUCTION

Nominal Conc.	vessel no.										Mean day
	1	2	3	4	5	6	7	8	9	10	
Control	8	11	7	18	8	20	13	10	-	11	11.8
100.0mg/L	13	17	-	8	11	7	11	17	11	-	11.9

Table 4 MEAN CUMULATIVE NUMBER OF JUVENILES PRODUCED PER ADULT AND INHIBITION RATE DURING EXPOSURE

Nominal Conc.	DAY 1–6	7	8	9	10	11	12	13	14	15	16
Control	0.0	0.2	0.9	0.9	1.3	4.0	4.0	12.4	18.4	18.4	25.4
100.0mg/L	0.0	0.4	0.9	0.9	0.9	3.8	3.8	4.8	6.8	6.8	6.8

Nominal Conc.	DAY 17	18	19	20	21	mean+/-S.D.	Inhibition rate (%)
Control	39.1	39.4	43.8	64.2	66.6	66.6+/-39.72	-
100.0mg/L	31.6	31.6	31.6	66.1	66.1	66.1+/-16.85	0.8

Table 5 CUMULATIVE NUMBER OF JUVENILES PRODUCED PER ADULT DURING EXPOSURE

Nominal Conc.	vessel no.										Total
	1	2	3	4	5	6	7	8	9	10	
Control	51	71	42	24	109	7	114	66	-	115	599
100.0mg/L	39	74	-	51	57	78	92	64	74	-	529

NUMBER OF WINTER EGGS DURING EXPOSURE
none of winter eggs at Control and 100.0 mg/L
STATISTICS: F&t-test; Yukms StatLight #3 “Pairwise Comparisons “

Source : EA Japan

Test condition : Test Organism:
-supplier; National Institute of Environmental Studies (Japan)
-age; juvenile Daphnia magna less than 24hr old
–feeding during acclimation; *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual
–acclimation; 3 - 4weeks
–feeding during test; *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual
STOCK AND TEST SOLUTION AND THEIR PREPARATION:
-solvent; no solvent was used
-stock of solution; no data
REFERENCE SUBSTANCE: $K_2Cr_2O_7$ EiC_{50} (48hrs) = 0.60 mg/L
DILUTION WATER:
-source; medium on OECD Guide-line 211
-hardness; 254 mg/L as $CaCO_3$
-pH; 7.6
TEST SYSTEM
-concentration; 0, 100.0 mg/L
-renewal of test solution; 3 times a week
-exposure vessel type; 80 mL test solution in a 100 mL glass vessel
-number of replicates/individual per replicate; 10/1
-test temperature; 19 - 21 degree C
-intensity of irradiation; room light

-photoperiod; 16hr - 8hr light-dark cycle
DURATION OF THE TEST: 21days
TEST PARAMETER:
-parents; number of dead parental Daphnia magna per day and abnormal behavior and appearance
-juveniles; number of juveniles produced per adult, number of dead juveniles and aborted eggs
SAMPLING: daily during exposure
MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by GC

Test substance : KISHIDA CHEMICALS CO., LTD (Lot No. D12358J) purity >= 98%
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
09.01.2003 (27)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Remark : Pseudomonas aeruginosa and Chromobacterium sp., Bacteria isolated from soil and water samples around industrial sites were able to use methacrylamide as carbon source.
Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (22)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 1789 mg/kg bw
Species : Rat
Strain : Crj: CD (SD)
Sex : Male
Number of animals : 5
Vehicle : Water
Doses : 0 (Vehicle), 1315, 1512, 1739, 2000 mg/kg
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1999
GLP : Yes
Test substance : As prescribed by 1.1 - 1.4
Result : Symptoms:
-1512 mg/kg or more; staggering gait, salivation, irritability, soiled perioral fur, sitting position, orange yellow urine.
–1315 mg/kg or more; tremor and decrease in body weight.
Pathological lesions:
-2000 mg/kg; slight atrophy of spleen.
-1739 mg/kg or more; intracelial cell fragment in epididymis.
-1512 mg/kg or more; moderate degeneration or necrosis of Step1 spermatid, slight multinuclear giant cell in seminiferous tubule, moderate decrease of elongate spermatid and slight or moderate decrease of pachytene spermatocyte at stage VII-XII in testes, decrease of spermatoza in epididymis.
-1512 and 1739 mg/kg; slight necrosis in purkinje's cells and small testes.
-1512 mg/kg; slight vacuolar degeneration in molecular layer, slight degeneration of sciatic nerve fibers, moderate necrosis of neurocyte and slight gliosis in hippocampus, slight necrosis of neurocyte in amigdala nuclei.
-1315 mg/kg or more; slight necrosis of neurocyte in cerebellar nuclei.

Confidence limits (95%) with probit method: 1559 – 2844 mg/kg

Table 1 Number of dead animals at 0, 1, 2, 3 - 14days (mortality)

DOSE	0day	1day	2day	3-14day	mortality
0mg/kg	0	0	0	0	(0/0)
1315mg/kg	0	0	0	0	(0/0)
1512mg/kg	0	2	0	0	(2/5)
1739mg/kg	0	1	0	0	(1/5)
2000mg/kg	0	0	4	0	(4/5)

Source : MHW Japan
Test substance : Mitsui chemicals, Inc. (Lot No.710130), purity = 99.5%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.04.2002 (50)

Type : LD50
Value : = 1774 mg/kg bw
Species : Rat

Strain : Crj: CD (SD)
Sex : Female
Number of animals : 5
Vehicle : Water
Doses : 0 (Vehicle), 1315, 1512, 1739, 2000 mg/kg
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1999
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Result : Symptoms:
-1512 mg/kg or more; staggering gait, salivation, irritability, soiled perioral fur, sitting position, orange yellow urine.
–1315 mg/kg or more; tremor and decrease in body weight.
Pathological lesions:
-1739 mg/kg; slight necrosis in purkinje's cells, slight degeneration of sciatic nerve fibers.
-1512 mg/kg or more; slight atrophy of spleen.
-1315 mg/kg or more; slight necrosis of neurocyte in cerebellar nuclei.

Confidence limits (95%) with probit method: 1575 – 2212 mg/kg

Table 1 Number of dead animals at 0, 1, 2, 3 - 14days (mortality)

DOSE	0day	1day	2day	3-14day	mortality
0mg/kg	0	0	0	0	(0/0)
1315mg/kg	0	0	0	0	(0/0)
1512mg/kg	0	0	1	0	(1/5)
1739mg/kg	0	0	2	0	(2/5)
2000mg/kg	0	0	4	0	(4/5)

Source : MHW Japan
Test substance : Mitsui chemicals, Inc. (Lot No.710130), purity = 99.5%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.04.2002 (50)

Type : LD50
Value : = 1938 mg/kg bw
Species : Rat
Strain : Wistar
Sex : male
Number of animals : 5
Vehicle : CMC
Doses : 1000, 2000, 3000 mg/kg bw
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1986
GLP : Yes
Test substance : other TS: Batch Number; 86013, Purity; >= 90%
Method Treatment:
-Solvent; Carboxymethylcellulose-Na-solution (suspension: 4%)
–Test article Preparation; Homogeneity of the test article in the vehicle was maintained during treatment using a magnetic stirrer. The preparation was made immediately prior to dosing.
–Application volume; 10ml at 1000 and 2000mg/kg bw
20ml at 3000 mg/kg bw
Result Symptoms:
-1000 mg/kg; sedation

–2000 mg/kg; sedation, somnolence, ataxia, ventral body position or curved
body position and ruffled fur.
–3000 mg/kg; sedation, ataxia, ventral body position, latero-abdominal position and curved body position.
The surviving rats had recoverd within 2 to 8 obsrevation days.
Pathology:
-1000 mg/kg; Killed; Lung; dark-red mottled (1)
–2000 mg/kg; Dead; Lung; dark-red mottled (1) and dark-red discolored (1),
Stomach/Intestines; severe meteorism (1), enlarged meteorism (1)
Killed; No pathological changes
–3000 mg/kg; Dead; Lung; dark-red to black mottled (1), dark-red light mottled (2), dark-red discolored (2), Stomach; meteorism (2), filled with test article (5), Intestines; yellowish foamy mass (4), reddish and yellow contents (2), Liver; ventral light mottled (4)

Confidence limits (95%) with probit method: 1353 - 3015 mg/kg

Table Number of dead animals at 1, 2, 3, 4 - 15 days(mortality)

DOSE	1day	2day	3day	4-15day	mortality
1000 mg/kg	0	0	0	0	(0/0)
2000 mg/kg	0	1	1	0	(2/5)
3000 mg/kg	0	5	0	0	(5/5)

Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.
Reliability : (1) valid without restriction
Guideline study, GLP.
Flag : Critical study for SIDS endpoint
29.07.2002 (83)

Type : LD50
Value : = 1653 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals : 5
Vehicle : CMC
Doses : 1000, 2000, 3000 mg/kg bw
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1986
GLP : yes
Test substance : other TS: Batch Number; 86013, Purity; >= 90%
Method : Treatment:
-Solvent; Carboxymethylcellulose-Na-solution (suspension: 4%)
–Test article Preparation; Homogeneity of the test article in the vehicle was maintained during treatment using a magnetic stirrer. The preparation was made immediately prior to dosing.
–Application volume; 10ml at 1000 and 2000mg/kg bw
20ml at 3000 mg/kg bw
Result : Symptoms:
-1000 mg/kg; sedation and ruffled fur
–2000 mg/kg; sedation, somnolence, ataxia, ventral body position or curved
body position, ruffled fur and emaciation

–3000 mg/kg; sedation, ataxia, ventral body position, latero-abdominal position, curved body position, ruffled fur and lacrimation.
The surviving rats had recoverd within 2 to 8 obsrevation days.
Pathology:
-1000 mg/kg; Killed; Lung; dark-red mottled (1)
–2000 mg/kg; Dead; Lung; dark-red discolored (2), reddish discolored (2), Stomach; enlarged meteorism (2), enlarged (2), Small intestines; meteorism with yellowish contents (2)
Killed; No pathologic changes
-3000 mg/kg; Dead; Lung; dark-red discolored (5), Stomach; severe meteorism (3), cloudy fluid (2), Intestines; yellowish fluid (5)

Confidence limits (95%) with probit method: 1035 - 2226 mg/kg

Table Number of dead animals at 1, 2, 3, 4 - 15 days(mortality)

DOSE	1day	2day	3day	4-15day	mortality
1000 mg/kg	0	0	0	0	(0/0)
2000 mg/kg	0	0	4	0	(4/5)
3000 mg/kg	0	5	0	0	(5/5)

Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.
Reliability : (1) valid without restriction
Guideline study, GLP.
Flag : Critical study for SIDS endpoint
29.07.2002 (83)

Type : LD50
Value : = 1538 mg/kg bw
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: no data
Year : 1980
GLP : no data
Test substance : no data
Remark : Symptoms: neurotoxic effects
Source : Mitsui Chemicals, Inc.
Reliability : (3) invalid
Study without detailed documentation.
07.08.2002 (74)

Type : LD50
Value : = 1223 mg/kg bw
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: no data
Year : 1967
GLP : No data
Test substance : No data

Remark	:	Symptoms: The clinical observation of the deceased animals revealed damage to the central nervous system.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(4) not assignable Documentation insufficient for assessment.

23.04.2002 (39) (106)

Type	:	LD50
Value	:	= 1380 - 1950 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1963
GLP	:	No data
Test substance	:	No data
Remark	:	Symptoms: neurotoxic effects (including reeling, unrest, excitation and spasms, together with breathing difficulties. No abnormalities were reported on autopsy. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt

23.04.2002 (14)

Type	:	LD50
Value	:	= 1750 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1957
GLP	:	No
Test substance	:	No data
Remark	:	Deaths preceeded by anaesthetic-like state. No gross autopsy findings.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(4) not assignable Only abstract available.

03.06.1997 (76)

Type	:	other: ALD50
Value	:	ca. 1500 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	ALD (approximative lethal dose) Application: 1- or 10 % Methacrylamide in water Symptoms: gait disturbances, atonia, abnormal body position:

lying on the side, jumping convulsion; Deaths occured
1-4 days after lethal doses
Post observation period: 7 days

Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (7)

Type : other: threshold for acute nervous system effects
Value : = 200 mg/kg bw
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: no data
Year : 1980
GLP : no data
Test substance : no data
Remark : No further information available.
Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (74)

Type : LD50
Value : = 567 mg/kg bw
Species : Mouse
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: no data
Year : 1980
GLP : no data
Test substance : no data
Remark : Symptoms: neurotoxic effects
Source : Mitsui Chemicals, Inc.
Reliability : (3) invalid
Study without detailed documentation.
07.08.2002 (74)

Type : LD50
Value : = 475 mg/kg bw
Species : Mouse
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: no data
Year : 1967
GLP : no data
Test substance : no data
Remark : Symptoms: weakness, ataxia and tonic-clonic spasms
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (4) not assignable
Documentation insufficient for assessment.
23.04.2002 (39) (106)

Type : LD50

Value	:	= 451 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: determined according to Weil (1952)
Year	:	1981
GLP	:	no data
Test substance	:	no data
Remark	:	Number of animals: 16; 4 animals per dosage level Vehicle: 0.9 % saline Details were not reported.
Source	:	Röhm GmbH & Co. KG Darmstadt
Test substance	:	Purity: > 95 % (GC)
Reliability	:	(2) valid with restrictions

28.04.2002 (35) (78)

Type	:	LD100
Value	:	= 250 - 2500 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: Range-finding test
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Number of animals: 2 (male, NMRI-mice) per dose group Solvent: oleum arachidis 5 % Administration: stomach tube; 5 % Methacrylamide in peanut oil Effects: 250 mg/kg and 500 mg/kg: No neurotoxic symptoms. 1000 mg/kg and 2500 mg/kg: All animals died within 1 hour after administration. Symptoms: reduced activity and general reactions, increased giddiness and ataxia within 5 minutes of treatment; 2 animals of the highest dose group showed a reduced pain reflex. Subsequent examination showed intense haemorrhaging of the stomach and mucosa lining. Other organs were not affected. No signs of neurotoxicity were evident in mice given 250- or 500 mg/kg.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Test procedure in accordance with national standard methods with acceptable restrictions, Range-finding study, no GLP.

23.04.2002 (90)

Type	:	LD50
Value	:	= 1865 mg/kg bw
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1967

GLP	:	no data
Test substance	:	no data
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(4) not assignable Documentation insufficient for assessment.
23.04.2002		(39) (106)

Type	:	
Value	:	= 500 - 1000 mg/kg bw
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	Number of animals: 7; 5 animals 500 mg/kg-group and 2 animals 1000 mg/kg-group Administration: single administration by stomach tube; aqueous suspension (5- or 20 % Methacrylamide in water) Mortality: 500 mg/kg: 3 out of 5 animals died after administration. 1000 mg/kg: 1 out of 2 animals Symptoms: loss of appetite, balance and posture disturbances, lying on the side (abnormal body position) and in one case diarrhoea and tonic spasms. Haematological and clinical-chemical analyses were normal.
Source	:	Röhm GmbH & Co. KG Darmstadt
03.06.1997		(6)

Type	:	
Value	:	= 100 - 1000 mg/kg bw
Species	:	Cat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	ALD50 (approximative lethal dose) Number of animals: 6 (4 animals 1000 mg/kg-group; 2 animals 100 mg/kg-group) Administration: single administration by stomach tube; 0.5 %- (100 mg/kg) or 5 % Methacrylamide (1000 mg/kg) in aqueous solution. Symptoms: 1000 mg/kg: 2 of 4 cats died after 1-2 days but no findings on autopsy. Vomiting occured in 3 of 4 cats after adminstration. After several hours the cats developed neurotoxic symptoms (including trembling, balance disturbance and spastic gait). The symptoms of the surviving cats improved after 4-5 days and disappeared within 1-3 weeks. 100 mg/kg: There were no signs of toxicity in 2 cats given 100 mg/kg. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt
03.06.1997		(9)

Type	:	
Value	:	= 500 - 1000 mg/kg bw
Species	:	Dog
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	Number of animals: 2 (1 animal 1000 mg/kg-group; 1 animal 500 mg/kg-group) Administration: single administration by stomach tube; as 10 % Methacrylamide in aqueous solution. Symptoms: 1000 mg/kg: increased salivation, slight disturbance of gait, followed by vomiting, tremor and tonic- convulsions. Death after about 60 hours. 500 mg/kg: No mortality. Slightly increased salivation and disturbance of gait after dosing. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (8)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Value	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1955
GLP	:	No data
Test substance	:	No data
Remark	:	12 rats were exposed to a saturated atmosphere of Methacrylamide (temperatur: 20 degree C). No toxicological effects were observed.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Only summary available, without detailed documentation.

26.05.2000 (11)

Type	:	
Value	:	= .01 - .08 mg/L
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)

Method : other
Year : 1980
GLP : no data
Test substance : no data
Remark : Administration: The substance was heated to 50 degree C to obtain a mixture of vapours and aerosols of methacrylamide.
Symptoms: 0.01 mg/L-group: No adverse effects.
0.037 mg/L-group: decreased haemoglobin values and an increased level of sulfhydryl groups in the blood.
No further information available (sex, strain, number of animals).
Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (74)

Type :
Value : = .01 - .08 mg/L
Species : Mouse
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time : 4 hour(s)
Method : other
Year : 1980
GLP : no data
Test substance : no data
Remark : Administration: The substance was heated to 50 degree C to obtain a mixture of vapours and aerosols of Methacrylamide.
Symptoms: 0.0256 mg/L-group: decreased activity
0.037 mg/L-group: decreased activity, decreased haemoglobin values and an increased level of sulfhydryl groups in the blood.
No mortality was observed (all dose groups).
No further information available (sex, strain, number of animals).
Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (74)

Type : other: TCLo
Value : = .003 - .01 mg/L
Species : Human
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
Method : other: no data
Year : 1980
GLP : no data
Test substance : no data
Remark : Symptoms: Headache, lacrimation, disturbed sleep, irritatibility, increase of limp reflexes, tremor.
Neither the exposure period nor the composition of the mixture was indicated (Mixture of different components).
Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (74) (78)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LDLo
Value	:	> 1600 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1966
GLP	:	No
Test substance	:	No data
Remark	:	Number of animals: 10 Application: 4 hours applied to abdominal skin, 20 % and 10 % methacrylamide solution Vehicle (mixture): 60 % Ethanol (96 %ig; with 2 % Benzen) 20 % Propanol 20 % Water Symptoms: No mortality; temporary apathy just like the control group exposed with the vehicle. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (12)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 200 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other: no data
Year	:	1989
GLP	:	no data
Test substance	:	no data
Source	:	Röhm GmbH & Co. KG Darmstadt

23.04.2002 (72) (78) (105)

Type	:	LD100
Value	:	= 200 - 1200 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	

Method	:	other: Range-finding-Test
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Number of animals: 2 (female NMRI-mice) per dose group Administration: 2- or 4 % methacrylamide emulsion in oleum arachidis (peanut oil) Post observation period: 24 hours Symptoms: 200 mg/kg-dose group: No mortality and no neurotoxic effects 400 mg/kg-dose group: No mortality, dose-dependant neurotoxic effects 400 - 800 mg/kg: decreased activity and decreased pain reflexes, transient cyanose, giddiness, ataxia. These effects were reversibel after 3 hours. 800 mg/kg-dose group: No mortality, from 800 mg/kg additionally clonic convulsion, reduction of body temperature, pale skin, abnormal gait and posture. 1200 mg/kg-dose group: Mortality: 2 of 2 animals After 3 hours: Symptoms like the 800 mg/kg-dose group.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Test procedure in accordance with national standard methods with acceptable restrictions, Range-finding study, no GLP.

23.04.2002 (89)

Type	:	other: ALD50
Value	:	ca. 1300 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	ALD (approximative lethal dose) Administration: 1- or 10 % methacrylamide in aqueous solution Post observation period: 7 days Symptoms: disturbance of gait, loss of appetite, following lying on the side, salivation, narcosis, tremor, trembling convulsion. Those animals that survived were symptom-free after 2 days. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (7)

Type	:	other: ALD50
Value	:	ca. 450 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	

Method	:	other: no data
Year	:	1955
GLP	:	no data
Test substance	:	no data
Remark	:	ALD (approximative lethal dose) Post exposure observation time: 7 days Administration: 8 % Methacrylamide in aqueous solution Symptoms: giddiness, restlessness, excitation, difficulties in breathing, convulsion, slow recovery
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (11)

Type	:	other: ALD50
Value	:	ca. 500 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	s.c.
Exposure time	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	ALD (approximative lethal dose) Administration: single administration of 1 % or 10 % methacrylamide in aqueous solution Post observation period: 7 days Symptoms: difficulties in breathing, disturbance of gait, abnormal body position: lying on the side, loss of appetite and death after one day
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (7)

Type	:	other: ALD50
Value	:	= 360 mg/kg bw
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	no data
Remark	:	ALD (approximative lethal dose) Administration: 1- or 10 % methacrylamide in aqueous solution Post observation period: 7 days Symptoms: jerky breathing, atonia and narcosis. Death within 48 hours. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (7)

5.2.1 SKIN IRRITATION

Species : Rabbit
Concentration : .5 g
Exposure : Semiocclusive
Exposure time : 4 hour(s)
Number of animals : 3
Vehicle : Water
PDII : 0
Result : Not irritating
Classification : Not irritating
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1998
GLP : Yes
Test substance : As prescribed by 1.1 - 1.4
Result : Very slight erythema was noted at all treated skin site one hour after patch removal. Treated skin sites appeared normal at the 24-hour observation.

Table 1 Average score for all animals at 1, 24, 48, 72 hours

skin reaction	1hr	24hr	48hr	72hr
Erythema/Eschar	1.0	0.0	0.0	0.0
Oedema	1.0	0.0	0.0	0.0

Source : Mitsui Chemicals, Inc.
Test substance : Mitsui chemicals, Inc., Batch number; 710130
Reliability : (1) valid without restriction
29.04.2002 (68)

Species : Rabbit
Concentration : .5 g
Exposure : Semiocclusive
Exposure time : 4 hour(s)
Number of animals : 3
Vehicle : Other
PDII : 1.11
Result : slightly irritating
Classification : not irritating
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1988
GLP : Yes
Test substance : As prescribed by 1.1 - 1.4
Result : Very slight erythema was noted in one animal 1 to 72 hours after patch removal and in one animal 1 and 24 hours after patch removal. And well defined erythema was noted in one animal 1 to 72 hours after patch removal.
Very slight oedema was noted in one animal 1 hour after patch removal. They were reversible until day 7.

Table 1 Average score for all animals at 1, 24, 48, 72 hours

skin reaction	1hr	24hr	48hr	72hr
Erythema/Eschar	1.33	1.33	1.00	1.00
Oedema	0.33	0.00	0.00	0.00

Remark : Method: Directive 84/449/EEC, B.4 "Acute toxicity (skin irritation)"

Purity: > 98 %
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (1) valid without restriction
Guideline study, GLP.
09.01.2003 (92)

Species : Rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : not irritating
Classification :
Method : other: no data
Year : 1967
GLP : No
Test substance : no data
Remark : Chronic application of 1/10 or 1/20 of the LD_{50}
(LD_{50}: 1865 mg/kg, oral, in aqueous solution, rabbit)
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (4) not assignable
Documentation insufficient for assessment.
23.04.2002 (106)

Species : Rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : slightly irritating
Classification :
Method : Other: no data
Year : 1980
GLP : No
Test substance : no data
Remark : No further information available.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Russian study, study without detailed documentation.
23.04.2002 (74)

Species : Rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : slightly irritating
Classification :
Method : Other
Year : 1955
GLP : No
Test substance : no data
Remark : Method: 1g moist solid of Methacrylamide over 12 sq. cm. for

4 hours (Rohm & Haas, 1955).
Result: minor primary irritation.
No further information available

Source : Röhm GmbH & Co. KG Darmstadt
28.04.2002 (39)

Species : Rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : slightly irritating
Classification :
Method : other
Year : 1963
GLP : No
Test substance : no data
Remark : Method: A 50 % aqueous solution of methacrylamide was applied to the backs of rabbits.
Application period: 1, 5, 15 minutes or 20 hours.
Result: No signs of irritancy when the skin was examined after 24 hours or 8 days after 1-15 minutes of application.
After 20 hours of application the animals showed slight redness of the skin, which was reversible after 8 days.
The application to the rabbit ear over a period of 20 hours caused no irritancy.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (5)

Species : guinea pig
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : slightly irritating
Classification :
Method : Other: no data
Year : 1980
GLP : No
Test substance : no data
Remark : No further information available.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Russian study, study without detailed documentation.
23.04.2002 (74)

5.2.2 EYE IRRITATION

Species : Rabbit
Concentration : .1g
Dose :
Exposure time :
Comment : not rinsed

Number of animals : 3
Vehicle : none
Result : moderately irritating
Classification : Irritating
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Result : No acute toxic symptoms and no mortality were observed in all animals.
Opacity of cornea (grade 1) was noted in all animals 1 to 72 hrs after treatment.
Iridic irritation (grade 1) was noted in one animal at 24 hrs after treatment.
Grade 3 of conjunctival redness was noted in one animal at 1 hr, grade 2 was noted in two animals at 1 hr and all animals at 24 to 48 hrs. At 72hrs, grade 2 of conjunctival redness was observed in one animal and grade 1 in two animals.
Grade 2 of conjunctival chemosis was found in all animals at 1 hr, while grade 1 was noted in all animals at 24 hrs and one animal at 48 hrs.
All effects were completely reversible after 7 days.

Table 1 Average score for all animals at 1, 24, 48, 72 hours

Reaction	1hr	24hr	48hr	72hr
Cornea opacity	1.00	1.00	1.00	1.00
IRIS	0.00	0.33	0.00	0.00
Conjunctival				
Redness	2.33	2.00	2.00	1.33
Chemosis	2.00	1.00	0.33	0.00

Primary irritation score (1-72 h): 3.83 of 13

Remark : Method: Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"
Purity: > 98 %
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (1) valid without restriction
Guideline study, GLP.

09.01.2003 (93)

Species : Rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : Irritating
Classification :
Method : other: no data
Year : 1955
GLP : No
Test substance : no data
Remark : Application: 1 x 50 mm^3 powder
Symptoms: Redness and oedema as well as slight opacity after 1 - 24 hours.
Recovery of the symptoms: after 8 days; opacity not completely reversible.
No further information available.
Source : Röhm GmbH & Co. KG Darmstadt

03.06.1997 (11)

Species	:	Rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: no data
Year	:	1980
GLP	:	No
Test substance	:	no data
Remark	:	Symptoms: Hyperaemia of the mucous membranes and a profuse serous discharge from rabbits' eyes. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Russian study, study without detailed documentation.

23.04.2002 (74)

5.3 SENSITIZATION

Type	:	no data
Species	:	Human
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: case reports
Year	:	1960
GLP	:	No
Test substance	:	no data
Remark	:	5 patients who were in contact with 1 % methacrylamide (solvent not indicated). They were previously exposed to acrylamide and other acrylates or methacrylates. 2 out of the 5 patients showed a positive reaction after 72 hours. There were also positive reactions with acrylates. The authors don't distinguish between a irritative- and sensitzing reaction. 30 volunteers (control group) with normal skin reactions showed no positive reactions when tested with 1 %- or 5 % methacrylamide.
Source	:	Röhm GmbH & Co. KG Darmstadt

03.06.1997 (54)

Type	:	no data
Species	:	guinea pig
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	Other: no data
Year	:	1980
GLP	:	No
Test substance	:	no data
Remark	:	The animals were treated intracutaneously with Methacrylamide and were subsequently challenged.

Result: slightly sensitizing
No further information available.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Russian study, study without detailed documentation.

23.04.2002 (74)

Type : no data
Species : guinea pig
Number of animals :
Vehicle :
Result : not sensitizing
Classification : not sensitizing
Method : other: no data
Year : 1966
GLP : No
Test substance : no data
Remark : Application: Induction: 1 g, 20 x 24 hours, occlusiv
Challenge: Day 14: 10 % Methacrylamide in a mixture of 60 % Ethanol, 20 % Propanol and 20 % water
Number of animals: 6
Symptoms: Induction: Slight local redness of the skin.
Result: 0 of 6 animals sensitizied
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Only summary available, without detailed documentation.

03.06.1997 (12)

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : Rat
Sex : Male
Strain : Crj: CD (SD)
Route of admin. : Gavage
Exposure period : 28days
Frequency of treatm. : 7days/week
Post exposure period : 14 days
Doses : 0 (vehicle), 30, 100, 300 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL : = 30 mg/kg bw
Method : OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year : 1999
GLP : Yes
Test substance : as prescribed by 1.1 – 1.4
Remarks : STATISTICAL ANALYSIS
For comparison of grip strength of forelimb or hindlimb, splay of hindlimb, locomotor activity counts, body weights, food consumption, urinary quantitative analysis, hematology, blood chemistry and absolute or relative organ weights, Bartlett's test for homogeneity of variance was first performed. When variance was homogeneous, one-way ANOVA was used. If significant differences were observed, the differences between treated group and control group were examined by Dunnett's multiple comparison test. On the other hand, when variance was not homogeneous, Kruskal-Wallis's test was used. If significant differences were observed, the differences were examined by Mann-Whitney's U-test.

For comparison of functional observation scores and urinary qualitative analysis, Kruskal-Wallis's test was first performed. If significant differences were observed, the differences between treated group and control group were examined by Mann-Whitney's U-test.
Differences from control group were considered to be significant at $p<0.05$.

Result : Deaths did not occur for all animals.
Clinical observations:
-300 mg/kg/day; staggering gait, decrease in body weight ($p<0.01$), body weight gain, food consumption ($p<0.01$) and water consumption, ataxia, decrease in muscle tone, grip strength of forelimb ($p<0.01$).
-100 mg/kg/day or more; decrease in locomotor activity counts(100mg/kg; $p<0.05$, 300mg/kg; $p<0.01$).
-At the end of recovery period; staggering gait, decrease in body weight ($p<0.01$), and food consumption, ataxia, decrease in muscle tone, locomotor activity counts ($p<0.01$), grip strength of hindlimb ($p<0.01$), splay of hindlimb ($p<0.05$).
Hematological findings:
-300 mg/kg/day; decrease in hematocrit ($p<0.05$).
-100 mg/kg/day or more; decrease in hemoglobin and MCH (100mg/kg; $p<0.05$, 300mg/kg; $p<0.01$).
-30 mg/kg/day or more; decrease in MCV (30 and 100mg/kg; $p<0.05$, 300mg/kg; $p<0.01$).
-At the end of recovery period; increase in platelet ($p<0.01$).
Blood chemical findings:
-300 mg/kg/day; increase in albumin ($p<0.05$), decrease in alpha1- and alpha2-globulin ($p<0.05$) and ALP ($p<0.05$).
-At the end of recovery period; increase in albumin ($p<0.05$), A/G ratio ($p<0.05$), potassium ($p<0.05$) and inorganic phosphorous ($p<0.05$), decrease of total protein ($p<0.05$), glucose ($p<0.01$) and triglyseride ($p<0.05$).
Pathology (number of animals):
-300 mg/kg/day; dilation of lumen in bladder (3), dark redness of light lobus anterior (1) and dark red maculae of left anterior (1) in lungs.
-At the end of recovery period; white maculae of light middle and left anterior in lungs (1).
Organ weight
–300 mg/kg/day; decrease in absolute organ weight of the brain, lungs, heart, liver, and adrenals ($p<0.05$), spleen and pituitary gland ($p<0.01$). increase in relative organ weight of the brain, lungs, heart, liver, thyroids, testes and epididymides ($p<0.01$).
-100 mg/kg/day or more; increase in relative organ weight of the kidneys ($p<0.01$).
-At the end of recovery period; decrease in absolute organ weight of the heart, liver and epididymides ($p<0.05$), increase in absolute organ weight of the testes ($p<0.05$). increase in relative organ weight of the spleen, adrenals and epididymides ($p<0.05$), and brain, lungs, kidneys and testes ($p<0.01$).
Histopathology (number of animals):
-300 mg kg/day; slight swelling of axonal in the cerebellar peduncle (1), slight degeneration of sciatic nerve fibers (7), moderate cellular infiltration of neutrophil (2) and granuroma (1) in the lungs, slight cellular infiltration of neutrophil at lamina propria in the trachea (1) and slight hyperplasia of tubular pars nervosa in the pituitary gland (1).
-At the end of recovery period; slight swelling of axonal in the cerebellar peduncle (3), slight (4) or moderate (3) degeneration of sciatic nerve fibers, slight (1) or moderate (1) granuroma in the lungs, retention of step19 spermatids at stage IX and X in testis (1)

Source : MHW Japan

Test condition : TEST ORGANISMS: Age; 5weeks old

Weight at study initiation; 152 – 183 g
Number of Animals: 7 per dose group
Administration: Vehicle; Purified water
Total volume applied; 5 mL/kg

Test substance : Mitsui chemicals, Inc., Lot No.710130, purity = 99.5%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2003 (51)

Type : Sub-acute
Species : Rat
Sex : Female
Strain : Crj: CD (SD)
Route of admin. : Gavage
Exposure period : 28days
Frequency of treatm. : 7days/week
Post exposure period : 14days
Doses : 0 (vehicle), 30, 100, 300 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL : < 30 mg/kg bw
Method : OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year : 1999
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Remarks : STATISTICAL ANALYSIS
For comparison of grip strength of forelimb or hindlimb, splay of hindlimb, locomotor activity counts, body weights, food consumption, urinary quantitative analysis, hematology, blood chemistry and absolute or relative organ weights, Bartlett's test for homogeneity of variance was first performed. When variance was homogeneous, one-way ANOVA was used. If significant differences were observed, the differences between treated group and control group were examined by Dunnett's multiple comparison test. On the other hand, when variance was not homogeneous, Kruskal-Wallis's test was used. If significant differences were observed, the differences were examined by Mann-Whitney's U-test.
For comparison of functional observation scores and urinary qualitative analysis, Kruskal-Wallis's test was first performed. If significant differences were observed, the differences between treated group and control group were examined by Mann-Whitney's U-test.
Differences from control group were considered to be significant at $p<0.05$.
Result : Deaths did not occur for all animals.
Clinical observations:
-300 mg/kg/day; staggering gait, decrease in food consumption ($p<0.01$) and water consumption, ataxia and decrease in muscle tone.
–100 mg/kg/day or more; decrease in body weight gain.
–30 mg/kg/day or more; decrease in locomotor activity counts (30 and 100mg/kg; $p<0.05$, 300mg/kg; $p<0.01$).
-At the end of recovery period; staggering gait, decrease in body weight ($p<0.01$) and food and water consumption, ataxia, decrease in muscle tone,
locomotor activity counts ($p<0.05$) and grip strength of hindlimb ($p<0.01$).
Hematological findings:
-300 mg/kg/day; decrease in hematocrit ($p<0.05$) and hemoglobin.
-At the end of recovery period; increase in platelet($p<0.05$) and PT ($p<0.05$).
Blood chemical findings:
-300 mg/kg/day; increase in albumin and triglyceride($p<0.05$), decrease in alpha1-globulin, urea nitrogen ($p<0.05$), creatinine ($p<0.05$) and ALP.

-At the end of recovery period; increase in ALP ($p<0.05$), potassium ($p<0.01$), inorganic phosphorous ($p<0.01$) and chlorine ($p<0.05$), decrease of total protein ($p<0.01$) and glucose ($p<0.01$).
Pathology (number of animals):
-300 mg/kg/day; dilation of lumen in bladder (1).
-At the end of recovery period; dilation of light renal pelvis in kidneys (1) and
cyst in ovaries (1).
Organ weight
–300 mg/kg/day; decrease in absolute organ weight of the brain, lungs, heart, liver, spleen, pituitary gland and thymus (heart; $p<0.05$, others; $p<0.01$), increase in relative organ weight of the brain, lungs, heart, liver and kidneys ($p<0.01$).
-At the end of recovery period; decrease in absolute organ weight of the brain, liver, pituitary gland and ovaries ($p<0.01$), increase in relative organ weight of the brain, lungs, heart, kidneys, spleen, adrenals and thymus (thymus; $p<0.05$, others; $p<0.01$).
Histopathology (number of animals):
-300 mg kg/day; slight swelling of axonal in the cerebellar peduncle (2), slight degeneration of sciatic nerve fibers (7), slight granulation of muscular layer in the esophagus (1).
-At the end of recovery period; slight swelling of axonal in the cerebellar peduncle (5), slight (5) or moderate (2) degeneration of sciatic nerve fibers, slight dilation of renal pelvis in the kidney (1), slight cyst in the pituitary gland (1) and uterus (1).

Source : MHW Japan
Test condition : TEST ORGANISMS: Age; 5weeks old
Weight at study initiation; 128 - 154 g
Number of Animals: 7 per dose group
Administration : Vehicle; Purified water
Total volume applied; 5 mL/kg
Test substance : Mitsui chemicals, Inc., Lot No.710130, purity = 99.5%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2003 (51)

Type :
Species : Rat
Sex : no data
Strain : no data
Route of admin. : Inhalation
Exposure period : 16 weeks
Frequency of treatm. : no data
Post exposure period : no data
Doses : 3.2, 12.0 or 34.5 mg/m^3
Control group : Yes
NOAEL : = .0032 mg/L
Method : other: no data
Year : 1980
GLP : No
Test substance : no data
Remark : Number of animals: 24; 6 per dose group
Application: The substance was heated to 50 degree C to obtain a mixture of vapours and aerosols of Methacrylamide.
Result : 12 mg/m^3: After 12 weeks: Slightly increased aggressiveness of the animals; increase in summation threshold potential.
After 16 weeks: Reduced activity, increased startle reaction, increased aggressiveness, decreased body-weight and

biochemical changes inthe brain (increase in hydroxy-indol acetic acid and histidine levels).
34.5 mg/m^3: After 12 weeks: Reduced body weight, increased aggressiveness. Decrease in investigative activity (explorative behaviour) and moti-vated behaviour decrease in summation threshold indices.
After 16 months: Reduced activity, increased startle reaction, biochemical changes in the brain.
Autopsy: Slightly smaller testes, and tendency for reduced mobility of spermatozoa. Dystrophic changes in the liver, and brain (increase of biogenic in rat brain: tryptophan, serotonin, 5-hydroxyindol acetic acid and histidine.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Russian study, partial translation into English available.
23.04.2002 (47) (74)

Type :
Species : Rat
Sex : Male
Strain : other: Porton
Route of admin. : oral feed
Exposure period : 25 days
Frequency of treatm. : 10 x 50 mg/kg for 11 days, followed by 10 x 100 mg/kg for the next 14 days
Post exposure period : no data
Doses : 50 mg/kg (11 days); 100 mg/kg (14 days)
Control group : no data specified
Method : other: no data
Year : 1970
GLP : No
Test substance : No data
Remark : Number of animals: 6 per dose group
Cumulative dose: 1500 mg/kg
No further information available.
Result : Gait and stance appeared normal, and the hind-limb activity (tested by the ability to grasp a sloping bar) was unaffected. No neurotoxic effects.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.
23.04.2002 (4) (39)

Type :
Species : Rat
Sex : Male
Strain : Wistar
Route of admin. : drinking water
Exposure period : 60-90 days
Frequency of treatm. : Continuously
Post exposure period :
Doses : 6.93, 10.4, 15.6 or 23.5 mM (equivalent to about 140, 210, 320 or 480 mg/kg/d
Control group : Yes
NOAEL : Ca. 210 mg/kg bw
Method : Other: Rotarod Performance Test
Year : 1983
GLP : No data
Test substance : no data
Remark : Number of animals: 16; 4 per dose level

Result : From 15.6 mM the Rotarod Performance was reduced about 50 % (15.6 mM 2 out of 4 animals, 23.5 mM 4 out of 4 animals);
decreased body weight gain.
Dose-dependant neurotoxic effects:
Symptoms: Ataxia (i.e. weakness, and a tendency toward spreading and dragging of hindlimbs). Urinary incontinence was seen in animals showing severe clinical signs.
Histology after 90 days:
23.5 mM-group: Morphological changes in tibial and sural nerves, such as shrinkage and loss of myelinated fibres, myelin retraction, and corrugated myelin sheaths, were observed.
After 60 days: significante reduction of (3H)-Colchicin-binding toneurotublin in nerve tissues.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.

23.04.2002 (107)

Type : Chronic
Species : Rat
Sex : Male
Strain : Wistar
Route of admin. : drinking water
Exposure period : 4, 8, and 12 months
Frequency of treatm. : Other: no data
Post exposure period : 12 month in the longest case
Doses : 0, 200, 400, 800 and 1200 ppm
Control group : Yes
NOAEL : = ca. 9.1 mg/kg/day
Method : Other
Year : 1993
GLP : no data
Test substance : no data
Remark : Estimated methacrylamide intake by drinking water per unit body weight per day:

Methacrylamide concentration [ppm]	Methacrylamide intake [mg/kg/day]	
	Beginning 3 months	4-12 months
200	2.8 +/- 1.0 (a)	1.2 +/- 0.3
400	5.0 +/- 1.6	2.3 +/- 0.6
800	9.6 +/- 3.0	4.6 +/- 1.0
1200	15.2 +/- 4.4	7.1 +/- 1.6

(a) Mean +/- SD. Number of animals in each group was from 18 to 20.
These estimated intake were apparently incorrect. Re-calculated doses and calculation manner were on Appendix 1.

STATISTICAL ANALYSIS
For comparison of 3 or more groups, the differences between group means were first examined by one-way ANOVA and then by Dunnett's multiple comparison test. Differences were considered significant at $p<0.05$.
For comparison of 2 groups, Fisher's exact probability test were used.
Result : 1200 ppm: Body weight gain was slightly but insignificantly suppressed compared to control during the treatment period. Sympotoms of peripheral neuropathy including hindlimb weakness and abnormal gait

were detected.
800 and 1200 ppm: Walking performance on a rotating rod decreased significantly($p<0.05$).
More than 800 ppm: Group atropy of the gastrocnemius muscle was detected. Some rats showed a distension of the urinary bladder (1 animal in 800 ppm and 3 animals in 1200 ppm).
Water and food consumption were not different among control and treatment groups during the treatment period.
Hematogram did not change significantly. Dose-related increases in serum total cholesterol (1200ppm, $p<0.05$)and phospholipid content (1200ppm, $p<0.05$)and gamma –glutamyl transpeptidase activity were seen after 12 months, although the increase in the last item was not statistically significant. Rat urine after 12 months did not show any significant biochemical change.
During post-administration period, pigmentation of body fur due to urinary incotinence, and symptoms of neuropathy were advanced, especially in rats receiving the two higher doses.
No significant differences in absolute or relative organ weights were seen among either treatment or post treatment periods.

Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

09.01.2003 (3)

Type :
Species : Rat
Sex : no data
Strain : no data
Route of admin. : Dermal
Exposure period : 12 days
Frequency of treatm. : 12 x 4 hours
Post exposure period : no data
Doses : 200 mg/rat (10 % aqueous solution) or 400 mg/rat (20 % aqueous solution)
Control group : Yes
Method : other: no data
Year : 1966
GLP : no data
Test substance : no data
Remark : Vehicle: mixture of: 60 % Ethanol; Purity: 96 % with 2 % Benzene
20 % Propanol and 20 % Water
Number of animals: 10
Result : All animals survived the exposure with methacrylamide.
Symptoms: Apathy and temporary reeling.
No further information available.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
03.06.1997 (12)

Type :
Species : Rat
Sex : male/female
Strain : no data
Route of admin. : oral unspecified
Exposure period : 35 days or 95 days
Frequency of treatm. : Daily
Post exposure period : 68 days

Doses : 360-380 mg/kg/d (35 d); 43-44 mg/kg/d (95 d) in the drinking fluid (tea)
Control group : Yes
Method : other: no data
Year : 1967
GLP : No
Test substance : no data
Remark : Number of animals: 20; 10 male and 10 female
Result : Mortality in the control group: 5 out of 40 animals (day 5 – 106)
43-44 mg/kg/d: No substance-related effects.
360-380 mg/kg/d: After 14 days: Excitation, paralysis of hind-limbs, reduced body weight
Mortality: 9/ 20 (day 17-33) and another 3/20 (1-2 days after the last dose) and a further 3/20 died during the 68 days observation period.
The findings at autopsy were not different from those of the control animals.
50 days after the last administration all effects were completely reversible.
No further information available.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (4) not assignable
Only summary available.

03.06.1997 (7)

Type : Chronic
Species : Mouse
Sex : Male
Strain : other: ddY
Route of admin. : Drinking water
Exposure period : 4, 8 and 12 months
Frequency of treatm. :
Post exposure period : 12 months in the longest case
Doses : 0, 200, 400, 800 and 1200 ppm
Control group : Yes
NOAEL : = ca. 24.3 mg/kg/day
Method : other: no data
Year : 1993
GLP : no data
Test substance : no data
Remark : Estimated methacrylamide intake by drinking water per unit body weight per day:

Methacrylamide concentration [ppm]	Methacrylamide intake [mg/kg/day]	
	Beginning 3 months	4-12 months
200	5.1 +/- 1.3(a)	3.3 +/- 1.4
400	10.6 +/- 3.7	6.1 +/- 2.1
800	17.5 +/- 4.9	9.5 +/- 4.6
1200	20.2 +/- 6.2	19.3 +/- 9.8

(a) Mean +/- SD. Number of animals in each group was from 18 to 20.
These estimated intake were apparently incorrect. Re-calculated doses and calculation manner were on Appendix 1.

STATISTICAL ANALYSIS
For comparison of 3 or more groups, the differences between group mean weres were first examined by one-way ANOVA and then by Dunnett's multiple comparison test. Differences were considered significant at $p<0.05$.

For comparison of 2 groups, Fisher's exact probability test were used.

Result : 800 and 1200 ppm: Body weight gain was decreased significantly($p<0.05$). Symptoms of peripheral neuropathy including hindlimb weakness and abnormal gait were detected. Walking performance on a rotating rod decreased significantly($p<0.05$).
More than 800 ppm: Group atropy of thegastrocnemius muscle was detected. Some mice showed a distension of the urinary bladder (1 animal in 800 and 1200 ppm).
Water and food consumption were not different among control and treatment groups during the treatment period.
Hematogram did not change significantly. In mice, a high but dose-unrelated increase of multiple lung tumors, which were diagnosed histologically as alveolar type II adenoma, was observed to be greater in the treatment groups than in the control.
During post administration period, pigmentation of body fur due to urinary incotinence, and symptoms of neuropathy were advanced.
No significant differences in absolute or relative organ weights were seen among either treatment or post treatment periods.

Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.01.2003 (3)

Type :
Species : Mouse
Sex : male/female
Strain : other: CF1
Route of admin. : Gavage
Exposure period : 14 days
Frequency of treatm. : once a day
Post exposure period : no data
Doses : 125, 250 und 500 mg/kg/d
Control group : Yes
NOAEL : = 125 mg/kg bw
LOAEL : = 250 mg/kg bw
Method : other: 14 d oral toxicity
Year : 1979
GLP : No
Test substance : as prescribed by 1.1 - 1.4
Remark : Number of animals: 20; 10 male and 10 female animals per dose group
Application: oral per stomach tube as 1.25; 2.5 and 5 % in aqueous solution
The effects of the substance were compared with those of Acrylamide.
With Acrylamide neurotoxic symptoms occured at a dose of 50 mg/kg/d.

Result : 125 mg/kg/d: No adverse effects.
250 mg/kg/d and 500 mg/kg/d:
Reduced food intake, reduced body weight gain in week one at 500 mg/kg/d in week two at 250 mg/kg/d. Neurotoxic symptoms appeared about 2 days earlier in the 500 mg/kg/d group compared to the 250 mg/kg/d group and were more severe in the higher dose group: Disturbance of coordination, hind-limb splay, decreased righting reflex, ataxia, slight tremor, slight cyanosis.
500 mg/kg/d: Mortality: 10 out of 20 animals.
Pathology: Haemorrhages of the lungs in the high dose group.
No other pathological changes in the major organs.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions

Study well documented, meets generally accepted scientific principles, accepted for assessment.

23.04.2002 (82)

Type	:	
Species	:	Mouse
Sex	:	Male
Strain	:	other: ddY
Route of admin.	:	Gavage
Exposure period	:	8 - 10 weeks
Frequency of treatm.	:	twice a week
Post exposure period	:	
Doses	:	153 mg/kg in 0.9 % in NaCl solution
Control group	:	Yes
Method	:	other: no data
Year	:	1978
GLP	:	No
Test substance	:	no data
Remark	:	Number of animals: 5 Application: by stomach tube
Result	:	Ataxia of the hind-limbs and slight behavioural changes (aggressiveness, alertness) were observed. From the 7 th week: Reduction of rotarod performance about 50 % (ID_{50}= 1787 mg/kg). Normal testicular weights and body weight gain. No hematological changes. The treatment of the animals with phenobarbital (50 mg/kg, 5x per week, i.p.) one week before the methacrylamide-administration until the end of administration of methacrylamide reduced the neurotoxic effects of the substance.
Source	:	Röhm GmbH & Co. KG Darmstadt

30.04.2002 (35) (72)

Type	:	
Species	:	Rabbit
Sex	:	male/female
Strain	:	no data
Route of admin.	:	Gavage
Exposure period	:	maximal 10 1/2 weeks
Frequency of treatm.	:	5 d/w
Post exposure period	:	up to 3 months
Doses	:	100, 250 or 500 mg/kg
Control group	:	No
Method	:	other: no data
Year	:	1967
GLP	:	No
Test substance	:	no data
Remark	:	Number of animals: 6 Application: stomach tube; 0.1 % - 0.5 % as aqueous solution No further information available.
Result	:	Symptoms: 500 mg/kg: After 5 doses, one animal developed paralysis, loss of appetite, diarrhoea and trembling. Analysis of blood revealed an increase of left-shift leucocytes prior to the animals death after 10 doses. 250 mg/kg: After 35 applications: Parese and paralysis. 2 out of 3 animals died (2 male, 1 unspecified) or had to be killed after 46 and 52 doses. Both animals showed loss of appetite and had diarrhoea and paralysis. The 3 rdanimal also showed paralysis but survived 52 doses of methacrylamide and recovered from paralysis 3 months after the end of the

treatement with methacrylamide.
100 mg/kg: Both animals died after 17 and 20doses, but this appeared to be due injuries induced during intubation Both animals showed no signs of toxicity.
At all dose levels, urine analysis revealed evidence of slight kidney damage, but there were no findings on histopathological examination of the dead animals.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (3) invalid
Only summary available, documentation insufficient for assessment.
03.06.1997 (6)

Type :
Species : Rabbit
Sex : male/female
Strain : no data
Route of admin. : Dermal
Exposure period : 24 h bzw. 8 h
Frequency of treatm. : 1 x 24 h following 20 x 8 h (clipped or clipped and scarified)
Post exposure period : up to 6 weeks
Doses : Methacrylamide as 66 %-paste (1 g/animal)
Control group : Yes
Method : other: no data
Year : 1966
GLP : No
Test substance : no data
Remark : Number of animals: 3; 1 male and 2 female
Result : No toxic effects; no systemic toxicity; no skin effects.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
03.06.1997 (12)

Type :
Species : Rabbit
Sex : Male
Strain : no data
Route of admin. : Dermal
Exposure period : 8 h/d
Frequency of treatm. : 5 d/w
Post exposure period : 6 weeks
Doses : 21 x (20 % in vehicle; ca. 0.7 or 0.8 g/kg
Control group : Yes
Method : other: no data
Year : 1966
GLP : No
Test substance : no data
Remark : Vehicle: mixture of: 60 % Ethanol; Purity: 96 % with 2 % Benzene
20 % Propanol and 20 % Water
Number of animals: 3
No further information available.
Result : No signs of toxic effects.
The analysis of the blood and urine at regular intervals during the 6 week observation period reveald no abnormalities, no functional disturbance of the liver (serumg/Lutamate-pyruvate transaminase) or kidneys (blood urea) was found.
Autopsy: No signs of toxicity.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (12)

Type	:	
Species	:	Rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	Dermal
Exposure period	:	5 weeks or 12 weeks
Frequency of treatm.	:	daily 5 d/w
Post exposure period	:	7 weeks
Doses	:	0, 5, 50 (12 weeks) or 500 mg/kg/d (5 weeks)
Control group	:	Yes
NOAEL	:	= 50 mg/kg
Method	:	other: no data
Year	:	1975
GLP	:	No
Test substance	:	no data
Remark	:	Number of animals: 24 per dose group Site of administration: clipped dorsal skin Application: 0.5 % in aqueous solution with Triton X-165.
Result	:	Clincal signs of neurotoxicity in 15/23 animals at 500 mg/kd/d. First observed at day 23. Splaying and forward extention of the hindlimbs. The animals showed normal reflex reactions to pinching of the toes. The incidence and severity of the toxic signs steadily increased (5 weeks). The effects were reversible within 20 days after the last administration. No adverse effects were noted at 5 and 50 mg/kg/d. No abnormalities were observed in haematology, clinical chemistry, gross and microscopic pathology of the treated animals. All major organs, including brain, spinal cord and sciatic nerves were examined.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, accepted for assessment.

23.04.2002 (77)

Type	:	
Species	:	Cat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	Gavage
Exposure period	:	9 weeks
Frequency of treatm.	:	once a day; 5 d/w
Post exposure period	:	up to 7 months
Doses	:	4-45 x 100 mg/kg, 3-6 x 250 mg/kg or 2 x 500 mg/kg
Control group	:	
Method	:	
Year	:	
GLP	:	No
Test substance	:	no data
Remark	:	Number of animals: 15 Application: By stomach tube; 0.5 - 5 % as aqueous solution No further information available.
Result	:	Symptoms: loss of appetite, disturbance of gait, restlessness, spasm-like convulsions, excitation, balance disturbance, spastic pareses and paralysis. Isolated observations of vomiting, diarrhoea, rhinitis and hairloss. Mortality: 1/2 animals of the 500 mg/kg dose group 2/8 animals of the 250 mg/kg dose group 2/5 animals of the 100 mg/kg dose group Recovery of surviving animals after 3 to 7 months.
Source	:	Röhm GmbH & Co. KG Darmstadt

Reliability : (3) invalid
Only summary available, documentation insufficient for assessment.
03.06.1997 (9)

Type :
Species : Cat
Sex : no data
Strain : no data
Route of admin. : i.p.
Exposure period : 3 weeks
Frequency of treatm. : no data
Post exposure period : no data
Doses : concentration, which is steadily increasing from 30 – 120 mg/kg/d
Control group :
Method : other: no data
Year : 1980
GLP : No
Test substance : no data
Remark : Application: 10 % aqueous solution of Methacrylamide providing a total dose of 900 mg/kg over a 3-week period.
No further information available.
Result : No indication of neurotoxic effects.
Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (24) (72)

Type :
Species : Dog
Sex : no data
Strain : no data
Route of admin. : oral feed
Exposure period : no data
Frequency of treatm. : daily (because of convulsions unregulary intervals in dosing)
Post exposure period : 14 months
Doses : 1 x 500 mg/kg followed by 14x 200 mg/kg or 27 x 200 mg/kg
Control group : No
Method : other: no data
Year : 1967
GLP : No
Test substance : no data
Remark : Number of animals: 2
No further information available.
Result : After an initial dose of 500 mg/kg methacrylamide (no effects were seen) the first neurotoxic effects were observed after 2 and 4 doses of 200 mg/kg.
Symptoms: stiffness of the hind-limbs and over excitation.
Food consumption was reduced. One dog developed severe and prolonged tremors, particulary in the rear half of its body, that it was impossible to stand on its hind-legs. 14 months after treatement with methacrylamide, the dog still had slight ataxia. In the second dog, stiff-leggedness, over excitement and shaking progressed to spastic paresis after 28 doses. The animal eventually died in convulsion.
No specific changes were indicated on autopsy.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (3) invalid
Only summary available, documentation insufficient for assessment, only 2 test animals.
03.06.1997 (13)

Type :

Species : Dog
Sex : no data
Strain : no data
Route of admin. : Gavage
Exposure period :
Frequency of treatm. : up to 5 times per week
Post exposure period : >= 6.5 months
Doses : 200 – 500 mg/kg (1 - 5 % aqueous solution)
Control group : no data specified
Method : other: no data
Year : 1967
GLP : No
Test substance : no data
Remark : Number of dogs Administration

9	2-6 x 500 mg/kg
2	4 x 300 mg/kg
2	6 or 27 x 250 mg/kg
1	16 x 200-400 mg/kg

Result : The intoxication due to methacrylamide is unique in dogs:
Vomiting followed by over excitation, trembling and after higher doses tonic-clonic spasms and convulsions. Convulsions could be provoked by external stimuli. Spastic paresis is followed by phases of convulsions or occurred at lower doses without convulsions.
6 dogs died after 2-6 doses, another one died 6 1/2 months after the last application of methacrylamide and 2 animals were bitten to death by healthier animals.
It took several months for the surviving animals to recover from the symptoms.
Neuropathological findings in 1 dog after 23 days of dosing were largely normal. Only the orientation and spontaneous activity when eys were covered was reduced.
Clinical observation: Decreased body weight, slightly increased blood-urea levels and slightly pathological kidney damage was found. The ZNS of 1 dog was examined. There were no changes at the spinal cord, but the brain showed a slightly increased number of glial cells.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (3) invalid
Only summary available, documentation insufficient for assessment.

03.06.1997 (8)

Type :
Species : Dog
Sex : male/female
Strain : no data
Route of admin. : Oral unspecified
Exposure period : 7 months to ca. 2 1/2 years
Frequency of treatm. : up to 5 d/w
Post exposure period : up to 8 years
Doses : 100 following 200, 300, 8 or 9 x 200 following 4 x 300 mg/kg/d
Control group : Yes
NOAEL : = 100 mg/kg bw
Method : other: no data
Year : 1967
GLP : No
Test substance : no data
Remark : Repeated dosing of 100 mg/kg/d to dogs did not result in specific neurotoxicity. An increase in the dose to 200 mg/kg/d resulted in specific neurotoxic symptoms after only a few applications. The authors therfore

conclude that the effects to the nervous system in dogs are not cumulative.
Number of animals: 4
Administration: 1 or 5 % aqueous solution; stomach tube or in the feed (meat)

Result : The repeated administration of 100 mg/kg/d did not cause the typical neurotoxic effects (tremor, spastic parese and ataxia) in dog. In one animal, epileptiform convulsions were observed over relativly great time intervals. These symptoms could not be clearly related to the exposure with the test substance.
2 out of 4 animals died during the study (1 animal died after 7 months (unclear cause); another animal died after 16 months (it was bitten to death).
3 days after the last administration the two surviving dogs received daily 8- or 9 times 200 mg/kg. After the 6 th dosage, loss of appetite, followed by trembling (8 th dosage), spastic paresis of the hind-limbs and disturbed gait was observed.
40 days after the last administration of 200 mg/kg, the animals received 4 x 300 mg/kg on 4 consecutive days.
Symptoms: Spastic walk, which persisted. One of the animals died after 8 months.
After the third dosage of 300 mg/kg, the surviving animal developed the same spastic walk. After the 4 th dosage, it was lying on the side and developed tremor, spastic paresis of the hind-limbs and tonic-clonic cramps.
After 7 days, the animal recovered to a small extent.
The symptoms did not significantly change over a period of 8 years indicating an irreversible effect.
That shows that the neurotoxic effects were not reversible.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (3) invalid
Only summary available, documentation insufficient for assessment.

26.05.2000 (8)

Type :
Species : guinea pig
Sex : no data
Strain : no data
Route of admin. : Dermal
Exposure period : 4 weeks
Frequency of treatm. : 20 x 24 hr; 5 d/w
Post exposure period : 14 days
Doses : 1000 mg/kg (20 % in vehicle as a paste)
Control group : Yes
Method : other: no data
Year : 1966
GLP : no data
Test substance : no data
Remark : Number of animals: 10
Vehicle: mixture of: 60 % ethanol, Purity: 96 % with 2 % benzene
20 % propanol and 20 % water
No further information available.

Result : 4 animals died after 6 or 10 applications. Prior to death, a slight tremor was observed. Local effect: Slight skin irritation.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
03.06.1997 (12)

Type :

Species	:	other: rat, mouse and rabbit
Sex	:	no data
Strain	:	no data
Route of admin.	:	drinking water
Exposure period	:	no data
Frequency of treatm.	:	no data
Post exposure period	:	no data
Doses	:	0.05 – 1 mg/kg/d
Control group	:	no data specified
Method	:	other: no data
Year	:	1967
GLP	:	No
Test substance	:	no data
Result	:	A daily dose of 0.05 - 1.0 mg/kg decreased cholinesterase activity in blood, increased the concentration of ascorbic acid in kidneys, and decreased the conditioned reflexes of the tested animals. Liver and kidney function appeared normal from biochemical analysis, and histological examination of the internal organs (not specified) did notreveal any abnormalities. No further information available.
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(3) invalid Russian study, documentation of the method used insufficient for assessment.

23.04.2002 (106)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA100, TA1535, TA98 and TA1537, Escherichia coli WP2 uvrA
Test concentration	:	-S9 mix; 0, 313, 625, 1250, 2500, 5000 ug/plate +S9 mix; 0, 313, 625, 1250, 2500, 5000 ug/plate
Cycotoxic concentr.	:	Toxicity was not observed up to 5000 ug/plate
Metabolic activation	:	with and without
Result	:	Negative
Method	:	Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year	:	1999
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	OECD Guide-line 471
Source	:	MHW Japan
Test condition	:	System of testing: -Metabolic activation system; S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone. Administration: -Number of replicates; 2 -Plate per test; 3 –Application; pre-incubation –Solvent; distilled water –Positive control groups and treatment; -S9mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98,WP2uvrA) Sodium azide (TA1535) 9-Aminoacridine (TA1537) +S9mix; 2-Aminoanthracene (five strains)
Test substance	:	Mitsui chemicals, Inc., Lot No.710130, purity >= 99.5%
Reliability	:	(1) valid without restriction

Flag	:	Critical study for SIDS endpoint
30.04.2002		(52)
Type	:	Chromosomal aberration test
System of testing	:	CHL/IU cell
Test concentration	:	-S9 mix (continuous treatment); 0, 0.23, 0.45, 0.90 (10mM) mg/mL -S9 mix (short-term treatment); 0, 0.23, 0.45, 0.90 (10mM) mg/mL +S9 mix (short-term treatment); 0, 0.23, 0.45, 0.90 (10mM) mg/mL
Cycotoxic concentr.	:	Toxicity was not observed up to 0.90 mg/mL (10mM).
Metabolic activation	:	With and without
Result	:	Negative
Method	:	Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year	:	1999
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	OECD Guide-line 473
Source	:	MHW Japan
Test condition	:	System of testing: -Metabolic activation system; S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone. Administration: -Plate per test; 2 –Solvent; distilled water – Positive control groups -S9 mix; Mitomycin C +S9 mix; Cychlophosphamide
Test substance	:	Mitsui chemicals, Inc., Lot No.710130, purity >= 99.5%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
30.04.2002		(53)
Type	:	Ames test
System of testing	:	S. typhimurium TA 1535, TA 1537, TA 98, TA 100, TA 1538
Test concentration	:	0 – 5000 mg/plate
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: no data
Year	:	1985
GLP	:	no data
Test substance	:	
Source	:	Röhm GmbH & Co. KG Darmstadt
Test substance	:	Purity: > 95 % (GC)
Reliability	:	(2) valid with restrictions Test procedure in accordance with international standard methods with acceptable restrictions.
23.04.2002		(32)
Type	:	Chromosomal aberration test
System of testing	:	CHL/IU cell
Test concentration	:	-S9mix (24hr direct method); 0, 0.250, 0.625, 1.25, 2.50, 5.00 (= 58.7mM) mg/mL -S9mix (48hr direct method);0, 0.20, 0.625, 1.25, 2.50, 5.00 (= 58.7mM) mg/mL +S9mix or -S9mix (metabolic activation method); 0, 0.625, 1.25, 2.50, 5.00 (= 58.7mM) mg/mL
Cycotoxic concentr.	:	Toxicity was not observed up to 5.00 mg/mL (= 58.7mM).
Metabolic activation	:	with and without
Result	:	Positive
Method	:	Guidelines for screening mutagenicity testing of chemicals, JAPAN

Year : 1993
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Remark : This test was performed according to GLP, but the concentration in which positeve responce was detected exceeded above maximum exposure level (= 10mM) in the guidelines for screening mutagenicity testing of chemicals, JAPAN.
Result : IN THE DIRECT TEST (24hr and 48hr treatment):
-frequency of structural aberrations at the high dose (5.00mg/mL = 58.7 mM) was significantly greater than that of the negative control group. The types of structural aberrations consisted mainly of gaps and chromatid breaks. At the dose levels less than 2.50 mg/mL was not significantly different from the negative control group.

Table 1 Frequency of structural aberrations

Treatment time	24hr	48hr
Negative Control	1.0%	1.5%
Methacrylamide		
0.200mg/mL (= 2.35mM)	-	1.0%
0.250mg/mL (= 2.94mM)	0.5%	-
0.625mg/mL (= 7.34mM)	1.5%	0.5%
1.250mg/mL (= 14.7mM)	1.5%	3.5%
2.50mg/mL (= 29.4mM)	2.0%	4.5%
5.00mg/mL (= 58.7mM)	23.0%	21.0%

IN THE METABOLIC ACTIVATION METHOD WITH AND WITHOUT S9MIX
–frequency of structural aberrations at the all doses were not significantly different from that of the negative control group.

Table 2 Frequency of structural aberrations

Metabolic activation	without S9mix	with S9mix
Negative Control	2.5%	1.5%
Methacrylamide		
0.625mg/mL (= 7.34mM)	2.5%	0.5%
1.250mg/mL (= 14.7mM)	2.5%	1.0%
2.50mg/mL (= 29.4mM)	3.0%	1.5%
5.00mg/mL (= 58.7mM)	2.0%	0.5%

Source : Mitsui Chemicals, Inc.
Test condition : System of testing:
-Metabolic activation system; S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone.
Administration:
-Plate per test; 2
–Solvent; distilled water
–Positive control groups
direct method; Mitomycin C
metabolic activation method (+S9mix or –S9mix); Benzo(a)pyrene
Test substance : Mitsui chemicals, Inc., Lot No.304190, Purity >= 99%
Reliability : (2) valid with restrictions
This test was performed according to GLP, but sevral concentrations of exposure exceeded above maximum exposure level (= 10mM) in the

guidelines for screening mutagenicity testing of chemicals, JAPAN and OECD guide-line 473.

29.04.2002 (66)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	Mouse
Sex	:	Male
Strain	:	CD-1
Route of admin.	:	drinking water
Exposure period	:	
Doses	:	24, 80, 240 ppm corresponding to 4.5, 15.4, 49 mg/kg/d
Result	:	
Method	:	other: part of modified reproductive assessement by continuous breeding protocol
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No differences in early embryonic deaths or total postimplation deaths.
Result	:	Negative
Source	:	Röhm GmbH & Co. KG Darmstadt
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, accepted for assessment, GLP.
Flag	:	Critical study for SIDS endpoint

23.04.2002 (73)

5.7 CARCINOGENICITY

Species	:	Mouse
Sex	:	Female
Strain	:	CD-1
Route of admin.	:	Gavage
Exposure period	:	2 weeks
Frequency of treatm.	:	6 times in 2 weeks
Post exposure period	:	28 weeks
Doses	:	25, 50, 100 mg/kg with TPA; 100 mg/kg without TPA
Result	:	
Control group	:	Yes
Method	:	other: Initation promotion study; Bull et al. (1984)
Year	:	1990
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Initiation-Promotion protocol: Number of animals: 40 per dose group Positive control: acrylamide Negative control: aqua bidest. Initiation period: 2 weeks Substance administration; 3 times per week by gavage 2 weeks without treatment. Promotion period: dermal adminstration of 12-o-tetra- decanoylphorbol-13-acetat (TPA) 2.5 ug in 0.2 ml acetone. 3 times per week on the clipped interscapular region.

Total study duration: 52 weeks
Some doubts can be raised concerning the validity and reliability of the test system as acrylamide which had previously been reported to have initiating properties in a study conducted following the same protocol did not show a tumor initiating potential in this study.

Result : Clinical observations:
Skin irritations with thickening, scabbling, scale formation was observed in all TPA treated groups. These skin reactions are attributed to the promotor treatment. Methacrylamide treatment did not lead to any clinical symptoms which could be causally related to the administration of the test substance.
Pathology/ Histology: All major organs were examined. No increased numbers of neoplasms were seen in the methacrylamide treated groups with or without TPA promotion. Methacrylamide had no tumor initating potential in this study.

Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (4) not assignable
23.04.2002 (19) (85)

Species : Mouse
Sex : Male
Strain : other: ddY
Route of admin. : i.p.
Exposure period : 5 days
Frequency of treatm. : Daily (first group) or 5 times every second day (second group)
Post exposure period : 6 months
Doses : 200 mg/kg in aqueous solution
Result :
Control group : Yes
Method : Other: no data
Year : 1989
GLP : no data
Test substance : no data
Result : In the first dose group in 16 of 57 mice and in the second dose group in 8 of 38 mice, an increased number of lung adenoma were found. After 3 hours it was shown with radiolabelled 14C-methacrylamide that the highest concentrations of methacrylamide were found in the kidneys, followed by liver, blood, spleen and lungs.
Approx. 5 % of the radiolabelled methacrylamide in the lung was bound to the protein fraction. A direct alkylation of nucleosides in vitro was not observed. The lipid per-oxidation of the microsomes was neither affected in vitro nor in vivo.
Histopathology of tumors: All tumors were identified as adenoma resulting from alveolar type II epithelial cells.
Control group: After 6 months, 1 of 48 animals had a tumor.

Source : Röhm GmbH & Co. KG Darmstadt
23.04.2002 (46)

5.8 REPRODUCTIVE TOXICITY

5.8.1 TOXICITY TO FERTILITY

Type : One generation study
Species : Rat
Sex : Male/female
Strain : Crj: CD (SD)

Route of admin.	:	Gavage
Exposure period	:	males; 42days, females; from 14days before mating to day 3 of lactation
Frequency of treatm.	:	7days/week
Premating exposure period		
Male	:	14days
Female	:	14days
Duration of test	:	1 generation
No. of generation studies	:	
Doses	:	0 (vehicle), 12.5, 50, 200 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 12.5 mg/kg bw
NOAEL F1 offspring	:	= 50 mg/kg bw
Method	:	OECD Guide-line 421
Year	:	2001
GLP	:	Yes
Test substance	:	As prescribed by 1.1 - 1.4
Remarks	:	STATISTICAL ANALYSIS For comparison of copulation indices, fertility indices and rates of morphological anomaly, Fisher's exact probability test was used. For comparison of histopathological change, Mann-Whitney's U-test was used on data graded or one-tailed Fisher's exact probability test was used on total value in positive grade. For comparison of others, Bartlett's test for homogeneity of variance was first performed on data of each animal or on means in each litter. When variance was homogeneous, then one-way ANOVA was used, otherwise, Kruskal-Wallis's test was used. If significant differences were observed between treated group and control group, Dunnett's multiple comparison test was used. Differences were considered significant at $p<0.05$.
Result	:	<Parental data> MORTARITY: -200 mg/kg; 1/13 (males), 4/13 (females), and one female was sacrificed on becoming moribund. CLINICAL OBSERVATION: -200 mg/kg; dragging of hindlimbs, decrease of body weight (males; 8 - 43 day of administration, $p<0.01$, -22.9% at 43 day, females; 8 – 15 day of administration and 0-20 day of pregnancy and 4 day of lactation, $p<0.01$, -26.0% at 4day of lactation, 0 day of lactation, $p<0.05$), decrease in food consumption (males and females, $p<0.01$) –50 mg/kg; significantly decrease of body weight gain (males and females) and decrease of food consumption (males, $p<0.01$) HISTPATHOLOGY: -200 mg/kg; inflammation of the lung was observed, and reproductive organs were not affected (males and females). REPRODUCTIVE TOXICITY: -200 mg/kg; feritility and estrous cyclicity were not affected, copulation rate was decreased ($p<0.01$), delayed parturition and abnormal nursing were observed. <F1 offspring data> -200 mg/kg; decreased delivery index ($p<0.01$), birth index ($p<0.01$) and live birth index ($p<0.05$), low body weight at 0 day of lactation (males ;-13.2%, females ;-12.5%, $p<0.05$) and decreased viability ($p<0.01$). No morphological abnormalities were found in any pups.
Source	:	MHLW Japan
Test condition	:	TEST ORGANISMS: Age; 9weeks old

Number of Animals: 13 per dose group
Administration: Vehicle; water for injection
Total volume applied: 5 mL/kg

Test substance : Mitsui chemicals, Inc., Lot No.810160, Purity = 99%
Conclusion : NOAEL for systemic toxicity; 12.5 mg/kg/day in male and female
NOAEL for reproductive and developmental toxicity; 50 mg/kg/day
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.01.2003 (49)

Type : Two generation study
Species : Mouse
Sex : male/female
Strain : CD-1
Route of admin. : drinking water
Exposure period : 189 days, 98 days continuous breeding
Frequency of treatm. : Continuously
Premating exposure period
Male :
Female : premating: 7 days
Duration of test : 27 weeks
No. of generation studies :
Doses : F0: 24, 80 and 240 ppm corresponding to 4.5, 15.4, 49 mg/kg/d
F1: 24, 80 and 240 ppm corresponding to 6.8, 23.8,71.3 mg/kg/d for males and 8 69mg/kg/d for females
Control group : Yes
NOAEL parental : = 49 mg/kg bw
NOAEL F1 offspring : < 6.8 mg/kg bw
Method : other: modified reproductive assessment continuous breeding protocol
Year : 1992
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4
Remark : Number of animals (controls): 76: 38 female and 38 male
Number of animals: 36 or 38 per group (18 or 19 males and 18 or 19 females)
Result : F0: No substance related clinical or histopathological changes.
F1: Preweaning growth, survival, food and water consumption not affected.
No treatment related clinical signs, no effect on reproductive competence.
At 3weeks of exposure: Reduced hind-limb grip strength at 24, 80 and 240 ppm in males and females. Reduced fore-limbs grip strength at 80 and 240 ppm in males. Those effects were slight and disappeared since 5 weeks.
At 16 weeks of exposure: Reduced hind-limb grip strength at 240 ppm in females (slight).
No histopathological changes. Normal fertility.
No dominant lethality.
Source : Röhm GmbH & Co. KG Darmstadt
Mitsui Chemicals, Inc.
Test substance : Purity: 99 %
Reliability : (1) valid without restriction
Test procedure in accordance with national standard methods with acceptable restrictions, GLP.
Flag : Critical study for SIDS endpoint
23.04.2002 (23) (73)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Mouse
Sex	:	Female
Strain	:	CD-1
Route of admin.	:	Gavage
Exposure period	:	6-17. day of gestation
Frequency of treatm.	:	Daily
Duration of test	:	
Doses	:	60, 120, 180 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 60 mg/kg bw
NOAEL teratogen.	:	= 180 mg/kg bw
Method	:	other: as OECD Guideline No. 414
Year	:	1990
GLP	:	Yes
Test substance	:	
Remark	:	Number of animals: 15-30 per dose group Vehicle: destilled deionized water Adminstration: oral All animals were killed on gestational day 17 and examined for maternal body weight, implant status, fetal weight, sex and morphological development.
Result	:	Symptoms: - at 60 mg/kg/d: no adverse effects. - at 120 mg/kg/d: slight maternal effects, and clear evidence of developmental toxiocity observed as a decrease in mean fetal body weight per litter. - at 180 mg/kg/d: mild maternal effects, observed as an increase in relative liver weight, clear maternal effects, observed as an decrease in body weight gain, and clear evidence of developmental toxicity, observed as an increased proportion of dead implants per litter, and decreased mean fetal body weight per litter; no external, visceral and skeletal malformations of the fetuses. NOAEL: 60 mg/kg/d (No-Observed-Adverse-Effect-Level) for both maternal developmental toxicity NOAEL: 180 mg/kg/d (No-Observed-Effect-Level) for terato-genicity
Source	:	Röhm GmbH & Co. KG Darmstadt Mitsui Chemicals, Inc.
Test substance	:	Purity: 99 % (GC)
Reliability	:	(1) valid without restriction Comparable to guideline study.
Flag	:	Critical study for SIDS endpoint

30.04.2002 (30) (72)

Species	:	Mouse
Sex	:	Female
Strain	:	NMRI
Route of admin.	:	i.p.
Exposure period	:	11-15. of gestation
Frequency of treatm.	:	Daily
Duration of test	:	
Doses	:	90 mg/kg and 225 mg/kg in aqueous solution
Control group	:	no data specified
NOAEL teratogen.	:	= 90 mg/kg bw
Method	:	Other: no data
Year	:	1966
GLP	:	No

Test substance : No data
Remark : Number of animals: 7 or 12
i.p. application is not considered to be a relevant route for testing the teratogenic potential of the substance.
Result : Symptoms:
90 mg/kg: No maternal toxicity. Apparently no effect on litter size, fetal body
weight and length, number of resorptions or incidence of mal-formations.
25 mg/kg: Maternal toxicity: reduced body weight gain.
Fetotoxicity:
Reduction of fetal body weight and increased resorptions and abortions.
Malformations: 6 of 91 alive fetuses; 5 animals with cleft palates and 1 with hydroplastic malformations of the extremities and tail aplasia.
The observed effects were not significantly different from spontanous rates observed in mice of this strain.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Only summary available, comparable to guideline study with acceptable restrictions, GLP.

26.05.2000 (10)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : Cytotoxicity

Remark : In relatively high concentrations, methacrylamide showed cytotoicity towards primary cell cultures of embryonic rat brain enriched in nerve cells. This was demonstrated by a decreased cumulative glucose consumption (ED_{50} = 15 mM).
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (36)

Type : Cytotoxicity
Remark : Cytotoxicity of methacrylamide was studied in 2 clonal cell lines derived from the nervous system, mouse neuroblastoma N18TG-2 cells and rat Schwannoma RT4 cells. Cell cultures were incubated for 5 or 4 days, respectively, in the presence of various concentrations of the test substance.
The effects on growth and cell morphology were determined microscopically. Cell viability was assessed using the tryptan blue method. Dose related cytotoxicity was only observed at doses exceeding 1 mM in both test systems.
ED_{50}-values were 8 mM in N18TG-2 cells and > 20 mM in RT4 cells.
Source : Röhm GmbH & Co. KG Darmstadt
24.04.2002 (114)

Type : Cytotoxicity
Remark : The cytotoxic effects of methacrylamide on the embryos of the common freshwater rotifer Adineta vaga was studied.
When eggs were incubated for 5 to 6 days in the presence of methacrylamide, the percentage of the eggs hatched was depended on the concentration. The estimated approximate concentration required to kill 50 % of the embryos was 0.04 M methacrylamide.
This sequence is identical to that reported by Hayashi et al. (1989) for the cytotoxicity of methacrylamide towards cultured neuronal cells from brains of rat embryos.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.
03.06.1997 (36) (120)

Type : Distribution
Remark : After i.p. administration of 14C-methacrylamide to male ddY mice, radioactivity was determined in different organs 3 minutes after dosing.
The distribution of radioactivity in different tissues was as follows:

Blood	11.1 %
Cerebrum	2.4 %
Cerebellum	2.8 %
Lung	8.0 %
Heard	6.7 %
Liver	12.6 %
Kidney	33.2 %
Spleen	8.3 %
Testis	5.0 %
Gastrocnemius muscle	4.8 %

5 % of the radioactivity in the lung was bound to protein.
Source : Röhm GmbH & Co. KG Darmstadt
19.01.2000 (46)

Type : Metabolism
Remark : In vitro-metabolism of methacrylamide was studied using hepatic microsomes of untreated and phenobarbital induced male ddY mice. One metabolite was detected by GC analyses but could not be identified.
Rate constants for the metabolism were determined:
Km = 2 mM; Vmax = 2.75 nmole/mg proteine * min.
Phenobarbital induction increased the reaction rate about 2-fold suggesting a cytochrome P-450 dependent metabolism.
Methacrylamide also reacted with reduced glutathione in vitro when incubated in the presence of a mouse liver cytosol preparation containing glutathione transferases.
Source : Röhm GmbH & Co. KG Darmstadt
26.05.2000 (112)

Type : Metabolism
Remark : The rate constant for the 2 nd order reaction of methacryl-amide with glutathione (pH: 7.3 and Temp.: 37 degree C) without enzymatic catalysis was very low: k = 0.014 l*mol-1*min-1 suggesting that direct reaction with cellular nucleophiles is negligible.
Source : Röhm GmbH & Co. KG Darmstadt
15.02.2000 (33) (39)

Type : Metabolism

Remark : Biotransformation in vitro:
Methacrylamide did not bind to 2-desoxyadenosine or 2-desoxycytidine or thymidine in an in vitro reaction experiment (pH: 7.0; Temp.: 37 degree C) over 10 weeks.
Source : Röhm GmbH & Co. KG Darmstadt
15.02.2000 (46)

Type : Metabolism
Remark : Methacrylamide did not have an influence on lipid peroxidation in lung microsomes of male ddY mice or male Wistar rats.
Source : Röhm GmbH & Co. KG Darmstadt
15.02.2000 (46)

Type : Neurotoxicity
Remark : A study was made on the effects of methacrylamide on the resting potential of the isolated desheathead sciatic nerve of the isolated retina of a frog. Methacrylamide had no effect on the resting and compound action potential (sucrose gap method).
Testconcentration: 25 mM methacrylamide
Source : Röhm GmbH & Co. KG Darmstadt
24.04.2002 (17)

Type : Neurotoxicity
Remark : Male wistar rats were treated for 120 days with (23.5 mM corresponding to ca. 480 mg/kg) methacrylamide in drinking water. Signs of neurotoxicity were observed after 120 days of treatement (Ataxia and a tendency towards spreading and draging of hindlimbs). After terminal kill, the spinal cords
were removed and pellets enriched in neurofilamental proteins were prepared. The NF-proteins were isolated and separated by SDS-immunoblotting technique. A reduction in the degradation of neurofilament proteins, in paticular the NF68K-proteine, was observed in treated rats compared to controls.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (113)

Type : Neurotoxicity
Remark : Relatively high concentrations of methacrylamide inhibited the neurite growth from rat dorsal root ganglion (3-days old) in culture. The half-maximum inhibition concentration (I_{50}) was determined from dose-response curve.
I_{50} = 30 mM
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (111)

Type : Neurotoxicity
Remark : Neurite-extending chick dorsal root ganglion (DRG) cells were exposed to methacrylamide in vitro and then growth cones were examined for alterations in morphology and function. DRG explants were exposed to media containing up to 16.6 mM methacrylamide for 16 hours. No effects were noted as a consequence of treating the cultures with methacrylamide up to 16.6 mM.
Source : Röhm GmbH & Co. KG Darmstadt
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, accepted for assessment.
24.04.2002 (44)

Type : Neurotoxicity

Remark : Species: Sprague-Dawley rats
Sex: males
Number of Animals: 5 per group
Time of exposure: 6 h per day, 7 days per week, for 2 weeks maximum
Test concentrations: 0, 12, 60 and 300 mg/m³ (0,030; 12,8; 62, 6 and 286 mg/m³analytical concentrations)
Vehicle: air

Following 14 days of exposure, all animals were sacrified, the brain and testes were weighed and organ/body and organ/brain weight ratios calculated. Complete macroscopic postmortem examinations were conducted on all animals.
Microscopic examination of peripheral nerves and gonades were conducted on all animals from the air control and high exposure level animals.

Result : There were no test material effects seen with respect to clinical observation, body weights, food consumption, grip strength, organ weights, macroscopic postmortem examinations or microscopic postmortem examinations. An increase in water consumption was seen in the high exposure level animals in the second week of exposure, altough, the toxicological significance of this difference was unclear.

NOAEL: 286 mg/m³

Source : Röhm GmbH & Co. KG Darmstadt

Test substance : Purity: 99,2- >99,8 %

Reliability : (1) valid without restriction
Test procedure in accordance with national standard methods with acceptable restrictions, Range-finding study, no GLP.

24.04.2002 (15)

Type : Other: Distribution, Excretion

Remark : Distribution and Excretion
Distribution of radiolabelled ^{14}C-methacrylamide was studied in male Japanese white rabbits after i.v. administration (15 % in water). Radioactivity was determined in different tissues after 24 hours. The highest concentration of radioactivity were found in the liver, followed by serum, kidney, total blood and lung. Lower levels were observed in the heart, brain, sciatic nerve and muscle. Most of the radioactivity (86 % of the dose) was excreted with the urine within 24 hours. Expired ^{14}C-CO_2 was very low (1 %).

Absorption and distribution
Skin absorption:
Skin absorption of ^{14}C-methacrylamide was studied in male Japanese white rabbits under both occluded and unoccluded conditions (5 and 15 % in water, for 15 or 30 minutes). After 24 hours the majority of the radioactivity remained at the application site. Autoradiography of the treated skin showed an accumulation in the hair follicles. Small amounts of radioactivity were also found in the other tissues. The highest levels were observed in the liver while radioactivity in the other tissues was evenly distributed. Results with occluded administration did not differ significantly from those obtained without occlusion. Washing of the application site after 15 minutes resulted in decreased serum levels of radioactivity. After 24 hours 23 - 52 % of the administered radioactivity was excreted with urine suggesting that methacrylamide may be absorbed through rabbit skin relatively easy. Primary absorption sites seemed to be the hair follicles.

Absorption
Dermal absorption of ^{14}C-methacrylamide in male Wistar rats and male

ddY mice after direct administration of 5 or 15 % aqueous solution for 30 minutes was lower than in rabbits, when adjusted to the dose per unit body weight. The majority of the radioactivity remained in the skin. Only 3.7 to 5.7 % of the radioactivity was excreted in the urine of the rats after 24 hours. Urinary excretion was not determined in mice.

Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (34)

Type : Other: binding to amino acids
Remark : Binding of methacrylamide to phenylalanine and tryptophane was studied in vitro. Binding constants were 10.3 mM for phenylalanine and 36.8 mM for tryptophane.
The authors tried to link neurotoxic effects with possible reactions with neurotransmitters.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (108)

Type : Other: effects on enzyme activities in vitro
Remark : Different concentrations of methacrylamide were added to rat brain homogenates in vitro and the inhibition of enolases was determined (I_{50} varied between 6.2 and 6.7 mM for the different isoenzymes). No difference in enolase inhibition between neurotoxic and non-neurotoxic substrates was reported by the authors.
Source : Röhm GmbH & Co. KG Darmstadt
19.01.2000 (108)

Type : Other: enzyme inhibition eventually related to neurotoxicity
Remark : The effects of methacrylamide on mouse brain glycolytic enzymes and a purified bovine neuron specific enzyme preparation was studied by measuring the enolase activity in vitro.
Inhibition concentration: I_{50} = 6.60 mM (total enolase)
I_{50} = 6.80 mM (bovine neuron specific enolase)
Methacrylamide had no effect on mouse brain glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and phosphofructokinase (PFK) (studies were performed with isolated enzymes) up to concentrations of 3.0 mM.
Source : Röhm GmbH & Co. KG Darmstadt
03.06.1997 (109)

Type : Other: enzyme inhibition eventually related to neurotoxicity
Remark : The in vitro effect of methacrylamide on rat brain glycolytic enzymes activity was examined. In high concentrations the substance inhibited the glyceraldehyde-3-phosphate dehydrogenase (GAPDH).
Inhibition concentration: I_{50} = 16.2 mM
The phosphofructokinase (PFK) activity was not inhibited by methacrylamide.
Source : Röhm GmbH & Co. KG Darmstadt
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Appendix 1. Recalculation manner for doses mentioned in the Aratani's study

	Approximate average body weight during exposure period calculated from body weight curve (g)[a)]		**Average water intake during exposure period (ml/day)[b)]**		**Average re-calculated dose/body (mg/day)[c)]**		**Average re-calculated dose (mg/kg/day)[d)]**		**Original dose mentioned in the literature by Aratani (mg/kg/day)**	
dose(concentration)	Rats (Wistar)	Mice (ddY)	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice
control	630	44	14	5.7	0	0	0	0	0	0
200ppm(200mg/L)	605	47	14	5.7	2.8	1.14	4.6	24.3	2.8-1.2	5.1-3.3
400ppm(400mg/L)	613	46	14	5.7	5.6	2.28	9.1	49.6	5.0-2.3	10.6-6.1
800ppm(800mg/L)	574	38	14	5.7	11.2	4.56	19.5	120	9.6-4.6	17.5-9.5
1200ppm(1200mg/L)	531	31	14	5.7	16.8	6.84	31.6	220.6	15.2-7.1	20.2-19.3

a) Approximate average body weights during exposure period were calculated from the weight of paper cut off from figure 1 in the original literature for each dose

b) Following sentences were referred for Average water intake during exposure period. "Until approximately 10weeks after commencement of treatment, food and water intakes per weight were gradually decreased. After this period, food and water intake per weight became stable, and average water intake a day was 14±2 g for rats and 5.7±1.3 g for mice."

c) Average re-calculated dose/body (mg/day) = Test substance concentration in drinking water (mg/L)/1000× Average water intake during exposure period (ml/day)

Average re-calculated dose (mg/kg/day) = Average re-calculated dose/body (mg/day) /Approximate average body weight during exposure period calculated from body weight curve (g)×1000