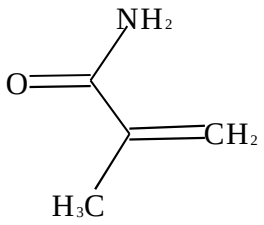
SIDS INITIAL ASSESSMENT PROFILE

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.