N-METHYLOLACRYLAMIDE

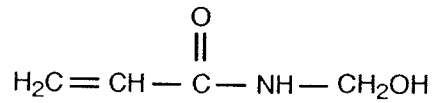
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 924-42-5
Deleted CAS Reg. No.: 90456-67-0
Chem. Abstr. Name: *N*-(Hydroxymethyl)-2-propenamide
IUPAC Systematic Name: *N*-(Hydroxymethyl)acrylamide
Synonyms: *N*-MAM P; *N*-methanolacrylamide; monomethylolacrylamide; NMA

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_7NO_2$ Relative molecular mass: 101.1

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White crystalline solid (Feuer & Lynch, 1953)
(*b*) *Melting-point*: 74–75 °C (Feuer & Lynch, 1953)
(*c*) *Spectroscopy data*: Infrared [10698], ultraviolet and nuclear magnetic resonance spectral data have been reported (US National Toxicology Program, 1989; Sadtler Research Laboratories, 1991).
(*d*) *Solubility*: Soluble in water (188 g/100 ml at 20 °C), methanol (149 g/100 ml at 30 °C), 90% ethanol (116 g/100 ml at 30 °C), isopropanol (53 g/100 ml at 30 °C) and *n*-butanol (42 g/100 ml at 30 °C) (American Cynamid Co., 1990a)
(*e*) *Stability*: Aqueous solutions are highly reactive. Upon heating in the presence of acids, they are rapidly polymerized to infusible resins (Feuer & Lynch, 1953). The stability of solutions is dependent mainly upon oxygen level, contaminants, storage temperature and pH (American Cynamid Co., 1990a).
(*f*) *Conversion factor*: $mg/m^3 = 4.13 \times ppm$[a]

[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

1.1.4 *Technical products and impurities*

N-Methylolacrylamide is available commercially as a 48% aqueous solution with the following specifications: assay, 48%; water, 51–54% (typically, 52%); pH, 5.5–6.5; free formaldehyde, 1.5–< 3 wt%; acrylamide, < 5.0 wt%; copper, 2 ppm max.; methylether of hydroquinone (inhibitor), 30 ppm; and specific gravity at 25 °C, 1.10 (National Starch and Chemical Corp., 1982; American Cyanamid Co., 1990a; Cytec Industries, 1993).

1.1.5 *Analysis*

No information was available to the Working Group.

1.2 Production and use

1.2.1 *Production*

Acrylamide reacts readily with formaldehyde to form *N*-methylolacrylamide (Updegraff *et al.*, 1978). Information available in 1991 indicated that *N*-methylolacrylamide was produced by two companies in Japan and one each in the Netherlands, the United Kingdom and the USA (Chemical Information Services Ltd, 1991). In Japan, about 900 tonnes were produced as powder and 250 tonnes as water solution in 1992 (Japan Petrochemical Industry Association, 1993).

1.2.2 *Use*

N-Methylolacrylamide is a bifunctional monomer with reactive vinyl and hydroxymethyl groups. Thermoplastic polymers can be formed by copolymerization of *N*-methylolacrylamide with a variety of vinyl monomers by emulsion, solution and suspension techniques. The resulting products, which have pendant hydroxymethyl groups, can undergo cross-linking under moderate conditions, permitting conversion of thermoplastic backbone polymers to thermoset materials at the point of use in the absence of an external cross-linking agent. Conversely, the hydroxymethyl group can be reacted with a substrate like cellulose and subsequently cross-linked by free-radical polymerization (US National Toxicology Program, 1989; American Cyanamid Co., 1990a,b).

The uses of *N*-methylolacrylamide range from adhesives and binders in papermaking and textiles to a variety of surface coatings and resins for varnishes, films and sizing agents (American Cyanamid Co., 1990a,b; Bucher *et al.*, 1990). It can be used in wet-strength and dry-strength agents for paper, in textile finishing agents for crease resistance, in antistatic agents, in dispersing agents, in cross-linking agents and in emulsion polymers.

1.3 Occurrence

1.3.1 *Natural occurrence*

N-Methylolacrylamide is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No data on human exposure to *N*-methylolacrylamide were available to the Working Group.

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 20 700 US employees were potentially exposed to a product containing *N*-methylolalcrylamide (US National Institute for Occupational Safety and Health, 1993). The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

1.4 Regulations and guidelines

There are no reported occupational standards or guidelines for *N*-methylolacrylamide (American Conference of Governmental Industrial Hygienists, 1993; ILO, 1993; UNEP, 1993). The US Food and Drug Administration (1993) permits use of polymers of *N*-methylolacrylamide in products in contact with food.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, were administered 0, 25 or 50 mg/kg bw *N*-methylolacrylamide (purity, approximately 98%) in deionized water by oral gavage on five days per week for 103 weeks. Surviving animals were killed at 113 weeks of age. The mean body weights of treated mice were up to 13% (males) and 25% (females) greater than those of vehicle controls. At the end of the experiment, survival rates in the control, low- and high-dose groups were 30/50, 20/50 and 21/50 males and 41/50, 35/50 and 33/50 females. The incidences of Harderian gland adenomas were increased in males given the low and high doses: control, 1/48; low-dose, 14/49; and high dose 29/50 ($p < 0.001$, logistic regression trend test) and in females given the high-dose: control, 5/47; low-dose, 8/45; and high-dose, 20/48 ($p < 0.001$, logistic regression trend test). The incidences of hepatocellular adenomas were increased in high-dose males and females: males—control, 8/50; low-dose, 4/50; and high-dose, 19/50 ($p < 0.05$, logistic regression trend test); females—control, 3/50; low-dose, 4/50; and high-dose, 17/49 ($p < 0.001$, logistic regression trend test). The incidences of hepatocellular carcinomas were marginally increased in treated male mice: control, 6/50; low-dose, 13/50; and high-dose, 12/50 ($p = 0.023$, incidental tumour test for comparison between low-dose and control). The incidence of hepatocellular adenomas and carcinomas (combined) showed a positive trend, and the incidences in high-dose males and females were higher than those in the vehicle controls: males—control, 12/50; low-dose, 17/50; and high-dose, 26/50 ($p < 0.001$, logistic regression trend test); females—control, 6/50; low-dose, 7/50; and high-dose, 17/49 ($p = 0.002$, logistic regression trend test). In high-dose males, the incidences of alveolar–

bronchiolar adenomas (control, 3/49; low-dose, 6/50; and high-dose, 11/50; $p < 0.05$, logistic regression trend test) and carcinomas were increased (control, 2/49; low-dose, 4/50; and high-dose, 10/50; $p < 0.05$, logistic regression trend test). The incidence of alveolar–bronchiolar adenomas and carcinomas (combined) showed a positive trend in male mice (control, 5/49; low-dose, 10/50; and high-dose, 18/50; $p < 0.001$, logistic regression trend test). The incidence of alveolar–bronchiolar adenomas and carcinomas (combined) was increased in high-dose females (control, 6/50; low-dose, 8/50; and high-dose, 13/49; $p < 0.05$, logistic regression trend test). The incidences of benign granulosa-cell tumours of the ovary were increased in treated groups (control, 0/50; low-dose, 5/45; and high-dose, 5/47; $p < 0.05$, logistic regression trend test) (US National Toxicology Program, 1989; Bucher *et al.*, 1990).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were administered 0, 6 or 12 mg/kg bw *N*-methylolacrylamide (purity, approximately 98%) in deionized water by oral gavage on five days per week for 103 weeks. Surviving animals were killed at 112 weeks of age. The mean body weights of treated rats were slightly lower than those of vehicle controls. At the end of the experiment, the survival rates in the control, low-dose and high-dose groups, respectively, were: males—28/50, 22/50 and 27/50; females, 35/50, 22/50 and 33/50. No neoplastic lesion was seen that was attributable to administration of *N*-methylolacrylamide (US National Toxicology Program, 1989; Bucher *et al.*, 1990).

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

After its intravenous administration at 140 mg/kg bw to rats, *N*-methylolacrylamide was distributed rapidly in total body water, with a first-order rate of elimination of 0.45/h from the blood compartment. Evidence for glutathione conjugation with *N*-methylolacrylamide in the bile was found in studies with the substance labelled in the methylene carbon, but no evidence was found for conversion to acrylamide *in vivo*. It is not known whether *N*-methylolacrylamide, like acrylamide, is also converted to an epoxide metabolite. No data were available on urinary metabolites (Edwards, 1975a).

N-Methylolacrylamide is an α,β-unsaturated carbonyl compound which reacts with nucleophilic atoms in Michael-type additions. It modified glycolytic enzymes in brain *in vitro* (Sakamoto & Hashimoto, 1985). Hashimoto and Aldridge (1970) found similar rates for the reaction of *N*-methylolacrylamide and acrylamide with glutathione *in vitro*; they also found

that both compounds react with protein sulfhydryls and haemoglobin in rats *in vivo*. The patterns of distribution of the two compounds between different tissues and subcellular organelles were also similar following oral administration to rats of equal doses of substances labelled in the carbonyl carbon.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

N-Methylolacrylamide given in large doses was found to be neurotoxic (Barnes, 1970). Edwards (1974, 1975b) confirmed the neurotoxicity of *N*-methylolacrylamide and demonstrated that its administration to rats hastened the onset of neurotoxicity induced by acrylamide. In mice (Hashimoto *et al.*, 1981) and rats (Tanii & Hashimoto, 1983), *N*-methylolacrylamide induced peripheral neuropathy of the same type as that induced by acrylamide but at a potency about 20–30% that of acrylamide. Neurotoxicity occurred in rats exposed to 25 mg/kg bw or more, as shown by both neurobehavioural and morphological examinations (US National Toxicology Program, 1989).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects (see also Table 1 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Few studies are available for evaluation. *N*-Methylolacrylamide did not induce gene mutation in *Salmonella typhimurium*. In single studies with Chinese hamster ovary cells *in vitro*, it induced chromosomal aberrations but only a weakly increased frequency of sister chromatid exchange. Micronuclei were not observed in bone-marrow cells of mice exposed *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

N-Methylolacrylamide is a bifunctional monomer used in the production of thermoplastic polymers and as a cross-linking agent in adhesives and binders for paper products and textiles. No data were available on occupational exposure to this compound.

Table 1. Genetic and related effects of *N*-methylolacrylamide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Hashimoto & Tanii (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Hashimoto & Tanii (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000 .0000	Zeiger *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Hashimoto & Tanii (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Hashimoto & Tanii (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Hashimoto & Tanii (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	(+)	(+)	250.0000	US National Toxicology Program (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	250.0000	US National Toxicology Program (1989)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	–		150.0000×2 ip	US National Toxicology Program (1989)

[a] +, positive; (+), weak positive; –, negative

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N-Methylolacrylamide was tested by oral gavage in one experiment in mice and one experiment in rats. In mice, it increased the incidences of Harderian gland adenomas, hepatocellular adenomas and carcinomas and alveolar–bronchiolar lung adenomas and carcinomas in animals of each sex and the incidence of benign granulosa-cell tumours of the ovary in females. In rats, no increase in tumour incidence was observed.

5.4 Other relevant data

N-Methylolacrylamide is absorbed by rats and mice after oral administration; no information was available regarding dermal application or inhalation. *N*-Methylolacrylamide administered to rats intravenously was distributed rapidly in body water; its distribution in tissues and subcellularly is similar to that of acrylamide. *N*-Methylolacrylamide reacts with glutathione, protein sulfhydryls and haemoglobin at rates similar to those of acrylamide, but it is not known if it is converted to acrylamide or an epoxide. Neurotoxicity developed in rats and mice exposed subchronically to *N*-methylolacrylamide.

No data were available on the genetic and related effects of *N*-methylolacrylamide in humans.

N-Methylolacrylamide did not induce micronuclei in mouse bone marrow *in vivo* but did induce chromosomal aberrations in Chinese hamster ovary cells *in vitro* and weakly increased the frequency of sister chromatid exchange. It was not mutagenic to *Salmonella typhimurium*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of *N*-methylolacrylamide.

There is *limited evidence* in experimental animals for the carcinogenicity of *N*-methylolacrylamide.

Overall evaluation

N-Methylolacrylamide *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 27–30.

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