MALONALDEHYDE (MALONDIALDEHYDE)

Data were last reviewed in IARC (1985) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

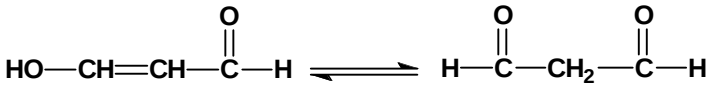
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 542-78-9
Chem. Abstr. Name: Propanedial
IUPAC Systematic Name: Malonaldehyde
Synonym: Malondialdehyde

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_3H_4O_2$ Relative molecular mass: 72.07

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Solid (needles) (United States National Library of Medicine, 1997)

(*b*) *Melting-point*: 72–74°C (IARC, 1985)

(*c*) *Stability*: Highly pure malonaldehyde is quite stable under neutral conditions but not under acidic conditions such as those used to prepare it by hydrolysis of its bis(dialkyl)acetal. Since malonaldehyde has pK_a = 4.46, it exists under physiological conditions as its conjugate base ($^-$O–CH=CH–CHO), which is relatively stable to self-condensation (IARC, 1985).

(*d*) *Conversion factor*: mg/m^3 = 2.95 × ppm

1.2 Production and use

Malonaldehyde is produced and used in small quantities, principally for research purposes (United States National Library of Medicine, 1997).

1.3 Occurrence

1.3.1 *Occupational exposure*

Exposure to malonaldehyde may occur in research laboratories.

1.3.2 *Environmental occurrence*

Malonaldehyde has been detected in the leaves of pea and cotton plants. It is found in many foodstuffs and can be present at high levels in rancid foods. It has been detected in fish meat, fish oil, rancid salmon oil, rancid nuts, rancid flour, orange juice essence, vegetable oils, fats, fresh frozen green beans, milk, milk fat, rye bread and in raw, cured and cooked meats (United States National Library of Medicine, 1997).

1.3.3 *Human tissues and secretions*

Malonaldehyde is found in human and animal tissue as an end-product of lipid peroxidation. It is also a side-product of prostaglandin and thromboxane biosynthesis. Malonaldehyde is present in blood platelets and in serum (IARC, 1985).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limit for malonaldehyde in workplace air.

No international guideline for malonaldehyde in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Malonaldehyde and its bis(dimethylacetal) and sodium salt were tested for carcinogenicity in mice by skin application. Its bis(dimethylacetal) and sodium salt were tested in mice by oral administration in drinking-water. The two studies by oral administration were inadequate for evaluation. After topical application, no increase in the incidence of skin tumours was observed in one study. In one two-stage mouse-skin assay, a high dose of malonaldehyde (possibly containing impurities) showed initiating activity. In two other two-stage assays using lower doses, no initiating or promoting activity was observed (IARC, 1985).

3.1 Oral administration

3.1.1 *Mouse*

Three groups of 50 male and 50 female B6C3F_1 mice, eight weeks of age, were administered 0 (vehicle control), 60 or 120 mg/kg bw malonaldehyde sodium salt (purity, 63–79% malonaldehyde sodium salt; 22–38% water; and 1% impurities as chloride and acetone) in distilled water by oral gavage on five days per week for up to 105 weeks. Survival rates at termination for males were 23/50 control, 19/50 low-dose and 14/50

high-dose ($p < 0.02$, Cox's method) and for females were 41/50 control, 38/50 low-dose and 30/50 high-dose. Body weight was slightly (less than 10%) lower than that of the vehicle controls in high-dose males during the second half of the study. Body weight was slightly (approximately 10%) higher than that of the vehicle controls in high-dose females during most of the study. No tumour type was increased in incidence in malonaldehyde-exposed mice compared with the vehicle controls (United States National Toxicology Program, 1988). [The Working Group noted the high mortality in high-dose males.]

3.1.2 *Rat*

Three groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were administered 0 (vehicle controls), 50 or 100 mg/kg bw malonaldehyde sodium salt (purity, 63–79% malonaldehyde sodium salt; 22–38% water; and 1% impurities as chloride and acetone) in distilled water by oral gavage on five days per week for up to 105 weeks, at which time the surviving animals were killed. Survival rates at termination for males were 37/50 control, 33/50 low-dose and 15/50 high-dose and for females were 37/50 control, 37/50 low-dose and 14/50 high-dose. The survival of the high-dose groups was significantly lower than that of the vehicle controls ($p < 0.001$). Mean body weights of high-dose male rats were 10–20% lower than those of the vehicle controls from week 33 to week 72 and 20–26% lower from week 72 to the end of the study. Mean body weights of low-dose male rats were 3–7% lower than those of vehicle controls from week 67 to the end of the study. Mean body weights of high-dose females were 10–20% lower than those of the vehicle controls from week 54 to week 72 and 21–36% lower from week 72 to the end of the study. The incidences of thyroid follicular-cell adenomas were 3/50 control males, 3/49 low-dose males and 9/50 high-dose males ($p < 0.05$) and 2/50 control females, 0/50 low-dose females and 5/50 high-dose females ($p < 0.05$); the incidences of follicular-cell carcinomas were 1/50 control males, 5/49 low-dose males and 5/50 high-dose males ($p < 0.05$) and 0/50 control females, 1/50 low-dose females and 2/50 high-dose females. Overall rates of thyroid follicular-cell tumours were 4/50 control males, 8/49 low-dose males and 13/50 high-dose males ($p = 0.015$) and 2/50 control females, 1/50 low-dose females and 7/50 high-dose females ($p = 0.03$). The incidences of pancreatic islet-cell adenomas in males were 0/49, 9/50 ($p < 0.002$) and 1/49 in the control, low- and high-dose groups, respectively (United States National Toxicology Program, 1988). [The Working Group noted the high mortality and the strong reduction in body weights in the high-dose males and females, indicating that the maximum tolerated dose was exceeded and also that the increased incidences of pancreatic islet-cell adenomas in males were not dose-related.]

4. Other Data Relevant to 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*

Two aldehyde dehydrogenases in the rat-liver cytosol fraction account for virtually all of the metabolizing activity for malonaldehyde (IARC, 1985).

Twelve hours after oral intubation of [1,3-^{14}C]malonaldehyde to rats, 60–70%, 5–15% and 9–17% of radioactivity was recovered in expired CO_2, faeces and urine, respectively (Siu & Draper, 1982).

After oral administration of malonaldehyde (158 mg/kg bw) to rats, increased quantities of formaldehyde, acetaldehyde, acetone and malonaldehyde itself were found in the urine. Additionally, methyl ethyl ketone, not found in control rats, was present in the urine of the animals that had received malonaldehyde (Akubue *et al.*, 1994).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Malonaldehyde, given in the drinking-water, induced morphological changes in the liver and mild dysplasia at all doses tested (2–500 mg/kg bw per day) in female ICR mice; pancreatic damage was observed at doses of 500 mg/kg bw per day (IARC, 1985). Histological changes were observed in the liver only of female ICR Swiss mice given 10–1000 μg/kg bw malonaldehyde in the drinking-water for one year, but no dose–response relationship was observed (Bird *et al.*, 1982a).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

Malonaldehyde reacts with DNA to form an adduct with 2′-deoxyguanosine which has been characterized as 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimido[1,2-α]purin-10(3H)-one (M_1G-dR) (Marnett, 1994). This adduct is present at quantifiable levels in DNA from many human tissues.

Chaudhary *et al.* (1994) found M_1G-dR in DNA from human liver samples (four males, two females) at levels ranging from 5 to 11 adducts/10^7 bases, using gas chromatography/electron capture negative chemical ionization mass spectrometry.

Leuratti *et al.* (1997) found M_1G-dR in DNA from human gastric biopsy samples at levels ranging from 1 to 9 adducts/10^8 normal nucleotides, using a high-performance liquid chromatography/^{32}P-postlabelling method (results presented as an abstract).

Fang *et al.* (1996) found that levels of M_1G-dR were influenced by dietary fats, with men and women consuming unsaturated fats having higher levels of the adduct in DNA from peripheral white blood cells than those who consumed saturated fats.

4.4.2 *Experimental systems* (see Table 1 for references)

Malonaldehyde induced mutation in bacteria that were either DNA repair competent or were sensitive to oxidative DNA damage. It had been suggested previously that all or part of the activity might be attributable to impurities, which occur as a result of malonaldehyde instability. However, specially purified or specially synthesized malonaldehyde continued to show mutagenic activity in *S. typhimurium his* D3052 (Basu & Marnett, 1983).

In one study in *Drosophila melanogaster*, malonaldehyde induced somatic mutations but not sex-linked recessive lethal mutations.

Malonaldehyde formed adducts with purified rat liver DNA, dAMP and dGMP *in vitro*; these adducts were observed with the ^{32}P-postlabelling technique (Wang & Liehr, 1995).

Malonaldehyde induced dose-dependent increases in sister chromatid exchanges but did not produce chromosomal aberrations in Chinese hamster ovary cells, but did induce chromosomal aberrations and micronuclei in rat primary skin fibroblasts.

At concentrations of malonaldehyde which produce reversion to histidine prototrophy in *Salmonella typhimurium* (TA100), characteristic adducts were found in bacterial DNA. The adducts were formed in a dose-dependent manner.

Injection of [^{14}C]malonaldehyde into male C57BL/6 mice resulted in covalent binding to liver DNA and haemoglobin.

Agarwal and Draper (1992) found background levels of malonaldehyde–guanine adduct in rat liver DNA, using high-performance liquid chromatography–fluorescence. Similar results were found by Vaca *et al*. (1992) and Wang and Liehr (1995) using ^{32}P-postlabelling. Chaudhary *et al*. (1994) used gas chromatography/electron capture negative chemical ionization mass spectrometry to measure background levels in rat liver. The levels were significantly elevated following administration of carbon tetrachloride (0.1 mL/kg bw), which induced lipid peroxidation (Chaudhary *et al*., 1994; Wang & Liehr, 1995).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Malonaldehyde is found in many foodstuffs and can be present at high levels in rancid foods. It is present as a lipid metabolite in human and animal tissues. It is probably used only as a research chemical.

Table 1. Genetic and related effects of malonaldehyde

Test system	Results[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ERD, *Escherichia coli rec* strains, differential toxicity	+	NT	72	Yonei & Furui (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	NG	Marnett & Tuttle (1980)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	NT	1000	Levin *et al.* (1982)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	NT	900	Marnett *et al.* (1985)
SA4, *Salmonella typhimurium* TA104, reverse mutation	+	NT	2520	Marnett *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	NG[d]	Mukai & Goldstein (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	NG	Marnett & Tuttle (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	NG[d]	Mukai & Goldstein (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	NG[d]	Mukai & Goldstein (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	NG	Marnett & Tuttle (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	NG	Marnett & Tuttle (1980)
SAS, *Salmonella typhimurium his* G46, reverse mutation	–	NT	NG[d]	Mukai & Goldstein (1976)
SAS, *Salmonella typhimurium his* C3076, reverse mutation	+	NT	NG[d]	Mukai & Goldstein (1976)
SAS, *Salmonella typhimurium his* D3052, reverse mutation	+	NT	NG[d]	Mukai & Goldstein (1976)
SAS, *Salmonella typhimurium* TA1975, reverse mutation	+	NT	500	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium* TA1977, reverse mutation	+	NT	500	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	+	NT	500	Shamberger *et al.* (1979)

Table 1 (contd)

Test system	Results[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAS, *Salmonella typhimurium his* C207, reverse mutation	+	NT	500	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium his* C3076, reverse mutation	+	NT	500	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium his* D3052, reverse mutation	+	NT	500	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium his* G46, reverse mutation	–	NT	4000	Shamberger *et al.* (1979)
SAS, *Salmonella typhimurium his* D3052, reverse mutation	+	NT	94	Marnett & Tuttle (1980)
SAS, *Salmonella typhimurium his* D3052, reverse mutation	+[c]	NT	72	Basu & Marnett (1983)
ECF, *Escherichia coli* H/r30 (uvr^+rec^+), forward mutation, streptomycin resistance	+	NT	144	Yonei & Furui (1981)
ECR, *Escherichia coli* H/r30 (uvr^+rec^+), forward mutation, arginine prototrophy	+	NT	144	Yonei & Furui (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		6125 feed	Szabad *et al.* (1983)
DMM, *Drosophila melanogaster*, somatic mutations	+		6125 feed	Szabad *et al.* (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	2.9	Yau (1979)
G51, Gene mutation, mouse lymphoma L5178Y cells, methotrexate resistance *in vitro*	+	NT	3.6	Yau (1979)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	15	Anderson *et al.* (1990)
MIA, Micronucleus test, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	7.2	Bird *et al.* (1982)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	3270	Anderson *et al.* (1990)
CIR, Chromosomal aberrations, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	7.2	Bird *et al.* (1982)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	7200	Vaca *et al.* (1992)
BID, Binding (covalent) to DNA from *Salmonella typhimurium* TA100 *in vitro*	+	NT	721	Sevilla *et al.* (1997)

Table 1 (contd)

Test system	Results[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Binding (covalent) to liver DNA, male C57BL/6 mice *in vivo*	+		22.5 ip × 1	Kautiainen *et al.* (1993)
BVP, Binding (covalent) to haemoglobin, male C57BL/6 mice *in vivo*	+		22.5 ip × 1	Kautiainen *et al.* (1993)
BVD, Binding (covalent) to DNA, C57/BL6 mouse liver *in vivo*	+		1.3 ip × 1	Vaca *et al*. (1992)

[a] +, positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal injection
[c] Highly purified malonaldehyde
[d] Confusion over actual dose applied

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Malonaldehyde sodium salt was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration. No increase in tumour incidence was found in mice. In rats, the incidence of follicular-cell tumours of the thyroid was increased in both sexes at the high dose and the incidence of pancreatic islet-cell adenomas was increased in low-dose males.

Malonaldehyde, its bis(dimethylacetal) and its sodium salts were tested for carcinogenicity in mice by skin application; no carcinogenic activity was observed.

5.4 Other relevant data

Background exposures to malonaldehyde occur in experimental animals and humans, as determined by the presence of specific DNA adducts in blood and other tissues. It is mutagenic to bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of malonaldehyde were available.

There is *limited evidence* in experimental animals for the carcinogenicity of malonaldehyde.

Overall evaluation

Malonaldehyde is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

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