ACRYLIC ACID

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

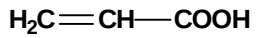
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 79-10-7

Systematic name: 2-Propenoic acid

1.1.2 *Structural and molecular formula and relative molecular mass*



$C_3H_4O_2$ Relative molecular mass: 72.06

1.1.3 *Physical properties* (for details, see IARC, 1979)

(*a*) *Boiling-point*: 141.0°C

(*b*) *Melting-point*: 14°C

(*c*) *Conversion factor*: $mg/m^3 = 2.94 \times ppm$

1.2 Production, use and human exposure

Acrylic acid is used primarily as an intermediate in the production of acrylates, which, in turn, are used in the production of polymers for coatings, paints, adhesives, paper and textiles. Exposure to unreacted acrylic acid may occur among consumers. The present recommendation by the American Conference of Governmental Industrial Hygienists (ACGIH) for the threshold limit value (TLV) is 5.9 mg/m^3 in workplace air. The previous TLV, before 1990, was 30 mg/m^3.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

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*

[1-^{14}C]Acrylic acid administered orally by gavage to rats (400 mg/kg) was well absorbed and rapidly and extensively metabolized, principally to exhaled $^{14}CO_2$, with 83% excreted in this form in 24 h. About 5% of the radioactivity was recovered in the urine and 9% in the faeces with 1.3% remaining in the tissues after 72 h (Winter & Sipes, 1993). Black *et al*. (1995) gave Fischer 344 rats 40 and 150 mg/kg bw [1-^{14}C]acrylic acid by gavage and obtained similar findings. Winter *et al*. (1992) gave 400 mg/kg bw [2,3-^{14}C]acrylic acid by gavage and, in comparison with their results with [1-^{14}C]acrylic acid, recovered 82% of the dose as $^{14}CO_2$, 5% in urine and 1% faeces, while 10% remained in the tissues after 72 h. In marked contrast, when DeBethizy *et al*. (1987) treated rats with 4, 40 or 400 mg/kg bw [2,3-^{14}C]acrylic acid by gavage, they recovered less as $^{14}CO_2$, approximately the same amounts in urine and faeces, and more in the tissues. The disposition of ^{14}C was a function of dose: as the dose increased, less was excreted, notably as $^{14}CO_2$ (65% of the dose at 4 mg/kg and 44% at 400 mg/kg) and more was retained in the tissues after 72 h (19% at 4 mg/kg and 25% at 400 mg/kg). The higher tissue retention of radioactivity from [2,3-^{14}C]acrylic acid is explicable by the entry of carbon atoms 2 and 3 into the tricarboxylic acid cycle, whereas carbon 1 can be oxidized immediately to CO_2.

The absorption and elimination patterns of orally administered acrylic acid (40 and 150 mg/kg bw) in mice were similar to those seen in rats (Black *et al*., 1995).

The percutaneous absorption of acrylic acid has also been examined in rats and mice. After application to the skin, approximately 73% of a dose of approximately 17 mg/kg bw (501 μg/cm^2) was lost by evaporation (Winter & Sipes, 1993). Of the remainder, 6% of dose was retained on or in the skin from the site of application and 16% was exhaled as $^{14}CO_2$. Urinary and faecal excretions were very minor routes (less than 1% and 2–4% of the dose, respectively).

These findings were confirmed and extended in rats and mice given doses of 10 and 40 mg/kg bw by Black *et al*. (1995), whose studies did not account for the complete balance of ^{14}C after dermal application (52–61% of dose, compared with 96% by Winter & Sipes, 1993).

The absorption of [^{11}C]acrylic acid after a 1 min inhalation exposure was studied in rat (Kutzman *et al*., 1982). After 1.5 min, 28% of the label was present in the snout of the animal and the major site of absorption was the gastrointestinal tract. Parallel studies of oral administration showed rapid and extensive absorption from the stomach and rapid metabolism and elimination as $^{11}CO_2$, which accounted for 60% of the dose within 1 h of dosing.

As stated above, various authors have confirmed the extensive conversion of acrylic acid to carbon dioxide in rats and mice treated orally or topically. In addition, urinary metabolites include 3-hydroxypropionic acid and the mercapturic acid *N*-acetyl-*S*-(2-carboxyethyl)cysteine and its *S*-oxide (DeBethizy *et al*., 1987; Winter *et al*., 1993).

The oxidation of acrylic acid can be rationalized in terms of the endogenous catabolism of propionic acid, in which acrylyl coenzyme A is an intermediate. This pathway is analogous with fatty acid β-oxidation, common to all species and, unlike the corresponding pathway in plants, does not involve vitamin B_{12}. 3-Hydroxypropionic acid has been found as an intermediate in the metabolism of acrylic acid *in vitro* in rat liver and mitochondria (Finch & Frederick, 1992). The CO_2 excreted derives from the carboxyl carbon, while carbon atoms 2 and 3 are converted to acetyl coenzyme A, which participates in a variety of reactions. The oxidation of acrylic acid is catalysed by enzymes in a variety of tissues (Black & Finch, 1995). In mice, the greatest activity was found in kidney, which was five times more active than liver and 50 times more active than skin (Black *et al*., 1993).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

In a study by Hellwig *et al*. (1993), Wistar rats of each sex were administered 150 or 375 mg/kg bw acrylic acid by gavage five times a week over three months. Fifty per cent of the animals in the low-dose group and 60% of the male and 90% of the female animals in the high-dose group died during the experiment. Pathological examination revealed a dose-dependent pronounced irritation of the forestomach and glandular stomach, purulent rhinitides and tubular necrosis of the kidneys.

After dermal exposure, 4% acrylic acid resulted in marked skin irritation in three strains of mice (McLaughlin *et al*., 1995), while 1% in acetone was tolerated, i.e. a less pronounced irritative effect was observed. In a commercial acrylic acid sample, α,β-diacryloxypropionic acid was identified as a strongly contact sensitizing constituent in guinea-pigs (Waegemaekers & van der Walle, 1984).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Klimisch and Hellwig (1991) exposed pregnant Sprague-Dawley rats by inhalation to 0, 40, 120 or 360 ppm [0, 118, 354 or 1060 mg/m^3] acrylic acid for 6 h per day during days 6–15 of gestation. At 360 ppm, eye and nose irritation, reduced body weight gain and reduced food consumption were observed in the animals. A slight effect on body weight gain was already observed at 40 ppm. No effects on the number of preimplantation losses, live fetuses or resorptions, and no indications for abnormalities or retardations in the fetuses above the background level were obtained.

Slott and Hales (1985) laparotomized pregnant Sprague-Dawley rats on day 13 of gestation and the uterus was exposed. Each embryo in one uterine horn received an intraamniotic injection of acrylic acid in 0.9% NaCl at doses of up to 1000 µg per fetus. The contralateral embryos received equivalent volumes of saline. The uterus was repositioned in the dam and the incision sutured. Dams were sacrificed on day 20 of gestation and the fetuses scored for survival, resorptions and external malformations. No significant increase in fetal malformations was observed, although a dose of 1000 (but not 100) µg per fetus enhanced the number of dead or resorbed fetuses significantly.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

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

Acrylic acid did not induce mutations in bacteria. It formed DNA adducts *in vitro*. It did not induce unscheduled DNA synthesis or cell transformation in rodent cells *in vitro*, or sex-linked recessive lethal mutations in *Drosophila*. It induced gene mutations and chromosomal aberrations in rodent cells *in vitro*. In single studies, acrylic acid given *in vivo* did not induce dominant lethal mutations in mice or chromosomal aberrations in rat bone marrow.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of acrylic acid were available.

No experimental data relevant to the carcinogenicity of acrylic acid were available.

Overall evaluation

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

6. References

Black, K.A. & Finch, L. (1995) Acrylic acid oxidation and tissue-to-blood partition coefficients in rat tissues. *Toxicol. Lett.*, **78**, 75–78

Table 1. Genetic and related effects of acrylic acid

Test system	Result[a]		Dose[b] (LEDor HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Zeiger *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Cameron *et al.* (1991)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Zeiger *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Cameron *et al.* (1991)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Zeiger *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Cameron *et al.* (1991)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Zeiger *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Cameron *et al.* (1991)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		2% feed	McCarthy *et al.* (1992)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		2% inj	McCarthy *et al.* (1992)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	630	McCarthy *et al.* (1992)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	–	–	2000	McCarthy *et al.* (1992)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LEDor HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	300	Moore *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	200	Cameron *et al.* (1991)
MIA, Micronucleus test, Syrian hamster embryo cells *in vitro*	–	NT	10	Wiegand *et al.* (1989)
CIM, Chromosomal aberrations, mouse lymphoma L5178Y cells *in vitro*	+	NT	450	Moore *et al.* (1988)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	1680	McCarthy *et al.* (1992)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	–	NT	25	Wiegand *et al.* (1989)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	–[c]		1000 po × 1	McCarthy *et al.* (1992)
DLM, Dominant lethal test, CD-1 mice *in vivo*	–[d]		324 po × 1	McCarthy *et al.* (1992)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	100 000	Segal *et al.* (1987)

[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; inj, injection; po, oral

[c] Results were also negative for rats treated with 5000 ppm in the drinking-water for five days.

[d] Results were also negative for mice treated with 162 mg/kg/bw by gavage for five days.

Black, K.A., Finch, L. & Frederick, C.B. (1993) Metabolism of acrylic acid to carbon dioxide in mouse tissues. *Fundam. appl. Toxicol.*, **21**, 97–104

Black, K.A., Beskitt, J.L., Finch, L., Tallant, M.J., Udinsky, J.R. & Frantz, S.W. (1995) Disposition and metabolism of acrylic acid in C3H mice and Fischer 344 rats after oral or cutaneous administration. *J. Toxicol. environ. Health*, **45**, 291–311

Cameron, T.P., Rogers-Back, A.M., Lawlor, T.E., Harbell, J.W., Seifried, H.E. & Dunkel, V.C. (1991) Genotoxicity of multifunctional acrylates in the *Salmonella*/mammalian-microsome assay and mouse lymphoma $TK^{+/-}$ assay. *Environ. mol. Mutag.,* **17,** 264–271

DeBethizy, J.D., Udinsky, J.R., Scribner, H.E. & Frederick, C.B. (1987) The disposition and metabolism of acrylic acid and ethyl acrylate in male Sprague-Dawley rats. *Fundam. appl. Toxicol.*, **8**, 549–561

Finch, L. & Frederick, C.B. (1992) Rate and route of oxidation of acrylic acid to carbon dioxide in rat liver. *Fundam. appl. Toxicol.*, **19**, 498–505

Hellwig, J., Deckardt, K. & Freisberg, K.O. (1993) Subchronic and chronic studies of the effects of oral administration of acrylic acid to rats. *Food chem. Toxicol.*, **31**, 1–18

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 47–72

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 56

Klimisch, H.-J. & Hellwig, J. (1991) The prenatal inhalation toxicity of acrylic acid in rats. *Fundam. appl. Toxicol.*, **16**, 656–666

Kutzman, R.S., Meyer, G.-J. & Wolf, A.P. (1982) The biodistribution and metabolic fate of [^{11}C]acrylic acid in the rat after acute inhalation exposure or stomach intubation. *J. Toxicol. environ. Health*, **10**, 969–979

Lijinsky, W. & Andrews, A.W. (1980) Mutagenicity of vinyl compounds in *Salmonella typhimurium*. *Teratog. Carcinog. Mutag.,* **1,** 259–267

McCarthy, K.L., Thomas, W.C., Aardema, M.J., Seymour, J.L., Putman, D.L., Yang, L.L., Curren, R.D. & Valencia, R. (1992) Genetic toxicology of acrylic acid. *Food chem. Toxicol.,* **30,** 505–515

McLaughlin, J.E., Parno, J., Garner, F.M., Clary, J.J., Thomas, W.C. & Murphy, S.R. (1995) Comparison of the maximum tolerated dose (MTD) dermal response in three strains of mice following repeated exposure to acrylic acid. *Food chem. Toxicol.*, **33**, 507–513

Moore, M.M., Amtower, A., Doerr, C.L., Brock, K.H. & Dearfield, K.L. (1988) Genotoxicity of acrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate in L5178Y mouse lymphoma cells. *Environ. mol. Mutag.,* **11,** 49–63

Segal, A., Fedyk, J., Melchionne, S. & Seidman, I. (1987) The isolation and characterization of 2-carboxyethyl adducts following in vitro reaction of acrylic acid with calf thymus DNA and bioassay of acrylic acid in female Hsd:(ICR)Br mice. *Chem.-biol. Interact.,* **61,** 189–197

Slott, V.L. & Hales, B.F. (1985) Teratogenicity and embryolethality of acrolein and structurally related compounds in rats. *Teratology*, **32**, 65–72

Waegemaekers, T.H.J.M. & van der Walle, H.B. (1984) α,β-Diacryloxypropionic acid, a sensitizing impurity in commercial acrylic acid. *Derm. Beruf Umwelt*, **32**, 55–58

Wiegand, H.J., Schiffmann, D. & Henschler, D. (1989) Non-genotoxicity of acrylic acid and *n*-butyl acrylate in a mammalian cell system (SHE cells). *Arch. Toxicol.*, **63,** 250–251

Winter, S.M. & Sipes, I.G. (1993) The disposition of acrylic acid in the male Sprague-Dawley rat following oral or topical administration. *Food chem. Toxicol.*, **31**, 615–621

Winter, S.M., Weber, G.L., Gooley, P.R., Mackenzie, N.E. & Sipes, I.G. (1992) Identification and comparison of the urinary metabolites of [1,2,3-$^{13}C_3$]acrylic acid and [1,2,3-$^{13}C_3$]propionic acid in the rat by homonuclear ^{13}C nuclear magnetic resonance spectroscopy. *Drug Metab. Disp.*, **20**, 665–672

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mutag.*, **9** (Suppl. 9), 1–110