CHLOROACETONITRILE

Data were last evaluated in IARC (1991)

1. Exposure Data

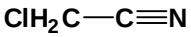
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 107-14-2

Systematic name: Chloroacetonitrile

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2H_2ClN Relative molecular mass: 75.50

1.1.3 *Physical properties* (for details, see IARC, 1991)

(*a*) *Boiling-point*: 126–127°C

(*b*) *Conversion factor*: $mg/m^3 = 3.09 \times ppm$

1.2 Production, use and human exposure

Halogenated acetonitriles are not produced on an industrial scale. Chloroacetonitrile has been used on a limited basis in the past as a pesticide. Several halogenated acetonitriles have been detected in chlorinated drinking-water in a number of countries as a consequence of the reaction of chlorine with natural organic substances present in untreated water. The only known route of human exposure is through chlorinated drinking-water (IARC, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Chloroacetonitrile was tested in a limited carcinogenicity study in female Sencar mice by skin application, in an initiation/promotion study in female Sencar mice by skin

application and in a screening assay for lung tumours in female strain A mice by oral administration. No skin tumour was produced after skin application in mice or in the initiation/promotion study, in which chloroacetonitrile was applied topically as six equal doses over a two-week period, followed by repeated doses of 12-*O*-tetradecanoylphorbol 13-acetate for 20 weeks. After oral administration, a small, significant increase in the proportion of mice with lung tumours and number of tumours per mouse was observed: control, 3/31 and 0.1; treated group (10 mg/kg bw, three times per week, eight weeks), 9/28 and 0.43 ($p < 0.05$) (IARC, 1991).

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*

Approximately 14% of a single oral dose to rats of 57 mg/kg bw of chloroacetonitrile was excreted in urine within 24 h as thiocyanate, the product of released cyanide metabolized by rhodanese (IARC, 1991).

Male Sprague-Dawley rats given intravenous injections of [2-^{14}C]chloroacetonitrile excreted in urine, faeces and expired air as $^{14}CO_2$, respectively, 51%, 2.7% and 12% of the dose in 12 h. Only 0.8% of the dose was exhaled as unchanged chloroacetonitrile. Computer-assisted image analysis of whole-body autoradiographs at various times up to 48 h indicated high, persistent levels of radioactivity in the thyroid, gastrointestinal tract, testes, brain and eye. Metabolic pathways were not studied in detail, but only 11% of the dose was excreted as CO_2 and no chloroacetonitrile was detected in the urine (Ahmed *et al*., 1991). In-vivo and in-vitro studies indicate that chloroacetonitrile reacts extensively with glutathione and causes significant decreases in glutathione levels in treated rats (Ahmed & Hussein, 1987; Lin & Guion, 1989).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Chloroacetonitrile did not induce γ-glutamyltranspeptidase-positive foci in rat liver (IARC, 1991).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

There were slight decreases in maternal weight gain during the treatment period and in the birth weights of the pups born to rats given chloroacetonitrile orally at a dose of 55 mg/kg bw daily on gestation days 7–21 (IARC, 1991).

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)

Chloroacetonitrile did not induce DNA damage or mutation in bacteria, whereas it induced sister chromatid exchanges and, weakly, DNA strand breaks in mammalian cell lines. Micronuclei were induced in the erythrocytes of newt (*Pleurodeles waltl*) larvae exposed for 12 days, but in mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology were induced.

5. Evaluation

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

There is *inadequate evidence* in experimental animals for the carcinogenicity of chloroacetonitrile.

Overall evaluation

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

6. References

Ahmed, A.E. & Hussein, G.I. (1987) Studies on the mechanism of haloacetonitriles acute toxicity. Interactions of dibromoacetonitrile (DBAN) with glutathione (GSH) and glutathione-*S*-transferase (GSHT) in rats (Abstract). *Toxicologist*, **7**, 452

Ahmed, A.E., Jacob, S. & Loh, J.P. (1991) Studies on the mechanism of haloacetonitriles toxicity: quantitative whole body autoradiographic distribution of [2-^{14}C]chloroacetonitrile in rats. *Toxicology,* **67,** 279–302

Bull, R.J., Meier, J.R., Robinson, M., Ringhand, H.P., Laurie, R.D. & Stober, J.A. (1985) Evaluation of mutagenic and carcinogenic properties of brominated and chlorinated acetonitriles: by-products of chlorination. *Fundam. appl. Toxicol.,* **5,** 1065–1074

Table 1. Genetic and related effects of chloroacetonitrile

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	–	–	1000	Le Curieux *et al.* (1995)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1500	Bull *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	–	+	30	Le Curieux *et al.* (1995)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1500	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1500	Bull *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	4	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblastic cell line *in vitro*	(+)	NT	NG	Daniel *et al.* (1986)
Micronucleus test, *Pleurodeles waltl* erythrocytes *in vivo*	+		1.25	Le Curieux *et al.* (1995)
MVM, Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	–		50 po × 5	Bull *et al.* (1985)
SPM, Sperm morphology, $B6C3F_1$ mice *in vivo*	–		50 po × 5	Meier *et al.* (1985)

[a] +, positive; (+), weak 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; NG, not given; po, oral

Daniel, F.B., Schenck, K.M., Mattox, J.K., Lin, E.L., Haas, D.L. & Pereira, M.A. (1986) Genotoxic properties of haloacetonitriles: drinking water by-products of chlorine disinfection. *Fundam. appl. Toxicol.,* **6,** 447–453

IARC (1991) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 52, *Chlorinated Drinking-Water; Chlorination By-Products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds,* Lyon, pp. 269–296

Le Curieux, F., Giller, S., Gauthier, L., Erb, F. & Marzin, D. (1995) Study of the genotoxic activity of six halogenated acetonitriles, using the SOS chromotest, the Ames-fluctuation test and the newt micronucleus test. *Mutat. Res.*, **341**, 289–302

Lin, E.L.C. & Guion, C.W. (1989) Interactions of haloacetonitriles with GSH and GST. *Biochem. Pharmacol.*, **38,** 685–686

Meier, J.R., Bull, R.J., Stober, J.A. & Cimino, M.C. (1985) Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. *Environ. Mutag.,* **7,** 201–211