DIMETHYLCARBAMOYL CHLORIDE

Data were last reviewed in IARC (1976) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

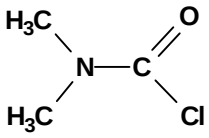
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 79-44-7

Chem. Abstr. Name: Dimethylcarbamic chloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_6NOCl Relative molecular mass: 107.6

1.1.3 *Physical properties* (for details, see IARC, 1976)

(*a*) *Boiling point*: 64°C at 27 kPa

(*b*) *Melting point*: –33°C

(*c*) *Conversion factor*: $mg/m^3 = 4.40 \times ppm$

1.2 Production and use

Dimethylcarbamoyl chloride has been produced since 1961. It has been used as an intermediate in the manufacture of a number of pharmaceuticals and pesticides (IARC, 1976).

2. Studies of Cancer in Humans

No death from cancer was reported in an investigation of 39 dimethylcarbamoyl chloride production workers, 26 processing workers and 42 ex-workers aged 17–65 years, who were exposed for periods ranging from six months to 12 years (IARC, 1976).

3. Studies of Cancer in Experimental Animals

Dimethylcarbamoyl chloride was tested for carcinogenicity by skin application and by subcutaneous and intraperitoneal injection in female mice of one strain; it induced local tumours (IARC, 1976).

3.1 Inhalation exposure

3.1.1 *Rat*

A group of 50 male Sprague-Dawley rats was treated by whole-body exposure to an atmosphere of 1 ppm [4.4 mg/m^3] dimethylcarbamoyl chloride for 6 h per day on five days per week for six weeks (i.e., 30 exposures). The experiment included two chamber control groups, each of 150 rats. The incidence of nasal cancer corrected for mortality at 480 and 600 days in the exposed group was 12% and 17%, respectively (Snyder *et al*., 1986). [This experiment was not fully reported.]

3.1.2 *Hamster*

A group of 100 male Syrian golden hamsters, eight weeks of age, was exposed by inhalation to 1 ppm [4.4 mg/m^3] dimethylcarbamoyl chloride for 6 h per day on five days per week for life. Two groups of 50 and 120 male hamsters served as sham-exposed and untreated controls, respectively. Neoplastic lesions of the nasal cavity were observed from 406 to 770 days. Squamous-cell carcinomas of the nasal cavity occurred in 50/99 hamsters in the treated group. No such tumour occurred in controls (Sellakumar *et al.*, 1980).

3.2 Skin application

Mouse: A group of 50 female ICR/Ha Swiss mice was treated by topical application with 2 mg dimethylcarbamoyl chloride in 0.1 mL acetone three times per week for up to 615 days. Three control groups, each of 50 mice, received acetone only for 575–665 days. No skin tumours arose in the control groups, whereas 32/50 mice in the treatment group developed tumours at the site of administration. Time to first tumour was 350 days and the tumours were identified as 1 papilloma, 27 squamous carcinomas and 4 keratoacanthomas (Van Duuren *et al*., 1987).

In the same study, two groups of 30 female ICR/Ha Swiss mice were injected subcutaneously with 0.43 or 4.3 mg dimethylcarbamoyl chloride in 0.1 mL tricaprylin once per week for 365 days and then observed for the remainder of their lifespan. An additional group of 50 mice received a subcutaneous dose of 4.3 mg per week for 365 days and were then killed. Three control groups consisting of either 30 or 50 (two groups) mice received tricaprylin alone once per week for up to 560–660 days. Two injection-site haemangiomas arose in one of the control groups. Injection-site tumours arose in 9/30, 22/30 and 42/50 of the treated groups, respectively (Van Duuren *et al*., 1987).

In the same study as the previous skin application experiment, 50 female ICR/Ha Swiss mice were treated by topical application with 5 mg dimethylcarbamoyl chloride in 0.1 mL

acetone on a single occasion, followed by three times weekly applications of phorbol myristyl acetate in 0.1 mL acetone [either 0.0025 or 0.005 mg per administration]. Two phorbol myristyl acetate control groups were available. Tumour incidences were: phorbol myristyl acetate, 0.0025 mg dose group, 0/50; 0.005 mg dose group, 3/30, which included 2 papillomas and 1 sarcoma; dimethylcarbamoyl chloride–phorbol myristyl acetate group 10/50, which included 2 papillomas, 7 squamous carcinomas and 1 keratoacanthoma (Van Duuren *et al.*, 1987).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group. However, dimethylcarbamoyl chloride is rapidly hydrolysed on contact with water to dimethylamine, HCl and CO_2.

4.2 Toxic effects

4.2.1 *Humans*

As previously summarized, one case of eye irritation and one of liver disturbances have been observed in workers exposed to dimethylcarbamoyl chloride. No other data were available to the Working Group (IARC, 1976).

4.2.2 *Experimental systems*

As previously summarized, dimethylcarbamoyl chloride when inhaled by rats damages the nasal mucous membrane, throat and lungs and causes breathing difficulties. It is irritant to the skin of rats and to skin and eye in rabbits. No evidence for sensitizing potential has been shown in guinea-pigs (IARC, 1976).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

Chromosomal analysis of peripheral lymphocytes from 10 people who had been occupationally exposed to dimethylcarbamoyl chloride (and diethylcarbamoyl chloride) for periods ranging from 4 to 17 years showed differences in the frequency of chromosomal aberrations (inclusive and exclusive gaps), when compared with a control group of 10 people matched for age, although statistical evaluation revealed no significant increase (Fleig & Thiess, 1978).

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

Dimethylcarbamoyl chloride induced DNA damage and mutation in bacteria. In fungi, it induced aneuploidy, mutation, gene conversion and DNA damage. Dimethylcarbamoyl chloride induced sex-linked recessive lethal mutations in *Drosophila melanogaster* in two studies, but not in a single feeding (aqueous solution) study, in which it would have been rapidly hydrolysed; it did not induce heritable translocations in two studies using administration by injection. Unscheduled DNA synthesis was not induced in primary cultures of rat hepatocytes. In other cultured mammalian cells, dimethylcarbamoyl chloride induced DNA strand breaks, chromosomal aberrations (in Chinese hamster ovary CHO cells, but not in rat hepatocytes), mutation at the *tk* locus of mouse lymphoma L5178Y cells and transformation in Syrian hamster embryo cells; conflicting results were obtained in studies of sister-chromatid exchange induction *in vitro*. *In vivo*, dimethylcarbamoyl chloride induced micronuclei but not sister chromatid exchanges in bone marrow cells of treated mice.

In conjunction with a carcinogenicity study (described in Section 3.1), male rats were exposed by inhalation to [^{3}H]dimethylcarbamoyl chloride (2.8–7.8 mCi inhaled). The association of radioactivity with DNA purified from the nasal mucosa was 11.0 ± 5.1 dpm/μg DNA per mCi inhaled (Snyder *et al*., 1986). *In vitro* reaction of dimethylcarbamoyl chloride with calf thymus DNA resulted in the formation of 6-dimethylcarbamyloxy-2′-deoxyguanosine and 4-dimethylaminothymidine (Segal *et al.*, 1982).

DNA from both rat nasal squamous carcinomas (2) and mouse skin squamous carcinomas (4) and fibrosarcomas (4) arising in dimethylcarbamoyl chloride-treated animals failed to transform NIH 3T3 cells by DNA transfection (Garte *et al.*, 1985).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to dimethylcarbamoyl chloride may occur during its manufacture and its use as an intermediate in the manufacture of a number of pharmaceuticals and pesticides.

5.2 Human carcinogenicity data

No deaths from cancer were reported in a small study of workers exposed for periods ranging from six months to 12 years.

5.3 Animal carcinogenicity data

Dimethylcarbamoyl chloride was tested for carcinogenicity in rats and hamsters by inhalation exposure, producing malignant tumours of the nasal cavity. It was also tested in mice by skin application and by subcutaneous and intraperitoneal injection, producing local tumours.

Table 1. Genetic and related effects of dimethylcarbamoyl chloride

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECB, *Escherichia coli* (*polA*), DNA strand breaks, cross-links or related damage; DNA repair	+	+	500	Tweats (1981)
ECD, *Escherichia coli pol* A/W3110-P3478, differential toxicity	+	NT	10	Rosenkranz & Poirier (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	500	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2000	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	+	500	Martire *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	250	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	250	Simmon & Sheperd (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	250	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	1250	Ashby *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167[c]	Dunkel *et al*. (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	500	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	25	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	50	Garner *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	2500	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	?	+	50[c]	Dunkel *et al*. (1984)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	500	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	MacDonald (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	(+)	–	2500	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	500	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167[c]	Dunkel *et al*. (1984)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	500	Simmon (1979a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	167[c]	Dunkel *et al*. (1984)
SA8, *Salmonella typhimurium* TA98, reverse mutation	+	+	500	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	500	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	500	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167	Dunkel *et al*. (1984)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	NT	500	Simmon (1979a)
ECR, *Escherichia coli* (other miscellaneous strains), reverse mutation	+	+	200	Mohn *et al*. (1981)
SSB, *Saccharomyces* species, RAD strains, differential toxicity	+	+	100	Sharp & Parry (1981a)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	–	–	160	Jagannath *et al*. (1981)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	+	NT	300	Sharp & Parry (1981b)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	NT	2400	Zimmermann & Scheel (1981)
SCH, *Saccharomyces cerevisiae* D3, homozygosis by mitotic recombination or gene conversion	(+)	(+)	50000	Simmon (1979b)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	–	+	107	Mehta & Von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	+	2	Loprieno (1981)
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	–	+	100	Parry & Sharp (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		0.2% feed	Würgler & Graf (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		10000 ppm inj	Yoon *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		2500 ppm inj	Foureman *et al.* (1994)
DMH, *Drosophila melanogaster*, heritable translocations	–		10000 ppm inj	Yoon *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocations	–		2500 ppm inj	Foureman *et al.* (1994)
DIA, DNA strand breaks, cross-links or related damage, Chinese hamster lung V79 cells *in vitro*	+	NT	321	Swenberg (1981)
URP, Unscheduled DNA synthesis, primary rat hepatocytes *in vitro*	–	NT	54	Probst *et al*. (1981)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	1200	Jotz & Mitchell (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	0.04%	Evans & Mitchell (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	100	Perry & Thomson (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	120	Natarajan & Van Kestern-Van Leeuwen (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO and lung DON cells *in vitro*	+	NT	1.7	Baker *et al*. (1983)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	20	Natarajan & Van Kestern-Van Leeuwen (1981)
CIR, Chromosomal aberrations, rat liver RL_1 cell line *in vitro*	–	NT	200	Dean (1981)
TCS, Cell transformation, Syrian hamster embryo cells	+	NT	0.1	Pienta *et al*. (1977)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1535 in Swiss-Webster mice *in vivo*	+		1000 po × 1	Simmon *et al*. (1979)
SVA, Sister chromatid exchange, CBA/J mouse bone-marrow cells *in vivo*	–		100 ip × 1	Paika *et al*. (1981)
MVM, Micronucleus test, ICR mice *in vivo*	+		160 ip × 1	Kirkhart (1981)
MVM, Micronucleus test, CD-1 mice *in vivo*	–		160 ip × 2	Tsuchimoto & Matter (1981)
MVM, Micronucleus test, $B6C3F_1$ mice *in vivo*	+		130 ip × 2	Salamone *et al*. (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[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; ip, intraperitoneal

[c] Results from four laboratories

5.4 Other relevant data

No data were available on the metabolism of dimethylcarbamoyl chloride, but it rapidly decomposes on contact with water to dimethylamine, hydrochloric acid and carbon dioxide.

Dimethylcarbamoyl chloride when inhaled by rats damages the nasal mucous membrane, throat and lung.

It has a wide spectrum of genotoxic activity, which is expressed as a result of its direct alkylating activity.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of dimethylcarbamoyl chloride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylcarbamoyl chloride.

Overall evaluation

Dimethylcarbamoyl chloride is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into consideration that dimethylcarbamoyl chloride is a direct-acting alkylating agent with a wide spectrum of genotoxic activity, including activity in somatic cells *in vivo*.

6. References

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