β-PROPIOLACTONE

Data were last reviewed in IARC (1974) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

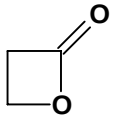
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 57-57-8

Chem. Abstr. Name: 2-Oxetanone

Synonyms: Hydracrylic acid, β-lactone; 3-hydroxypropionic acid, lactone; 3-hydroxypropionic acid, β-lactone; propanolide; 3-propanolide; propiolactone; 3-propiolactone; β-propionolactone

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_3H_4O_2$ Relative molecular mass: 72.06

1.1.3 *Chemical and physical properties of the pure substance*

(from American Conference of Governmental Industrial Hygienists (1992), unless otherwise noted)

(*a*) *Description*: Colourless liquid with a slightly sweetish odour (Budavari, 1996)

(*b*) *Boiling-point:* 162°C (Lide, 1997)

(*c*) *Melting-point:* –33.4°C (Lide, 1997)

(*d*) *Solubility:* Soluble in water (37 mL/100 mL at 25°C) with hydrolysis; miscible with acetone, chloroform, diethyl ether, ethanol and other common organic solvents (American Conference of Governmental Industrial Hygienists, 1992; Budavari, 1996; Lide, 1997)

(*e*) *Vapour pressure:* 452 Pa at 25°C; relative vapour density (air = 1), 2.5

(*f*) *Flash point:* 74°C, closed cup

(*g*) *Reactivity*: Polymerizes during storage

(*h*) *Explosive limits:* Lower, 2.9% by volume in air

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

1.2 Production and use

No information on the global production of β-propiolactone was available to the Working Group.

β-Propiolactone has been used as a vapour sterilant for plasma, vaccines, tissue grafts, surgical instruments and enzymes; as a vapour-phase disinfectant in enclosed spaces; and in organic synthesis. Its sporicidal action is used against vegetative bacteria, pathogenic fungi, and viruses. It has been used as an intermediate in the production of acrylic acid and esters (American Conference of Governmental Industrial Hygienists, 1992; United States National Library of Medicine, 1998).

1.3 Occurrence

No data were available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 1.5 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to β-propiolactone in workplace air and lists it as an animal carcinogen. Similar values have been used as standards or guidelines in many countries. Australia, Belgium, Finland, France, Germany, Sweden and Switzerland list β-propiolactone as a probable human carcinogen (International Labour Office, 1991).

No international guideline for β-propiolactone 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

β-Propiolactone was tested for carcinogenicity in mice following skin application or subcutaneous or intraperitoneal injection, and in rats following subcutaneous injection, producing local tumours. It is carcinogenic to mice after single-dose exposure. Oral administration to rats gave some indication of carcinogenic activity. The results obtained in Syrian hamsters and guinea-pigs are equivocal (IARC, 1974).

3.1 Inhalation exposure

Rat: A group of 50 male Sprague-Dawley rats [age unspecified] was exposed by whole-body inhalation to 10 ppm [30 mg/m^3] β-propiolactone [purity unspecified] for 6 h

per day on five days per week for six weeks. A control group of 150 rats was exposed to filtered air using the same exposure protocol. After treatment, animals were observed for lifespan. The mortality-corrected incidence of nasal cancer 480 days after the start of exposure was 60%. At the end of the experiment (around 720 days), all β-propiolactone-exposed rats had developed nasal cancer [histology unspecified]. No nasal cancer was observed in control rats (Snyder *et al*., 1986).

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.

4.2 Toxic effects

No data were available to the Working Group.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

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)

β-Propiolactone is a direct-acting alkylating agent that reacts with polynucleotides and DNA, mainly at N7 of guanine and N1 of adenine, to form carboxyethyl derivatives. It also forms adducts with the N^3 of cytosine and thymine (Hemminki, 1981; Lawley, 1984). It is genotoxic to a wide range of organisms *in vitro* and *in vivo.*

β-Propiolactone was mutagenic to bacteria. In yeast, it induced mitotic gene conversion, aneuploidy and mutations. It produced heritable translocations and sex-linked recessive lethal mutations in *Drosophila melanogaster*. *In vitro*, it induced cell transformation and gene mutations in human cells, and cell transformation, gene mutations, chromosomal aberrations and sister chromatid exchanges in mammalian cells.

In single studies, when given *in vivo*, β-propiolactone induced gene mutations in the stomach and liver in the Muta™ Mouse, and DNA strand breaks in rat liver and mouse skin keratinocytes. In a single study, it induced chromosomal aberrations in rat bone-marrow cells *in vivo*. β-Propiolactone bound covalently to mouse skin DNA and RNA *in vivo.* It induced chromosomal aberrations or micronuclei in oocytes, spermatids, hepatocytes and splenocytes in mice *in vivo.*

Table 1. Genetic and related effects of β-propiolactone

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage, *umu* induction, SOS repair test, DNA strand breaks, cross-links	+	NT	8.3	Nakamura *et al.* (1987)
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine	+	NT	3	Castellino *et al.* (1978)
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine	+	NT	2.9	Penman *et al.* (1979)
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine	NT	+	100	Skopek *et al.* (1981)
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine	+	NT	0.7	Skopek & Thilly (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	50	Anderson & Styles (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	3	Castellino *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	50	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	18	Drinkwater *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	37	Baker & Bonin (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Brooks & Dean (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	6.9	Garner *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation, fluctuation test	+	+	1	Hubbard *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	7.5	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	25	Martire *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Simmon & Shepherd (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Venitt & Crofton-Sleigh (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	36	Bartsch *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	91	Wattenberg *et al.* (1987)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	–	NG	Anderson & Styles (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	3	Castellino *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	50	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG	Baker & Bonin (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	1.5	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG	Garner *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	+	633 μg/m^3 vap.	Pincus *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	10	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	36	Bartsch *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	NG	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	+	NG	Baker & Bonin (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	NG	Brooks & Dean (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	?	–	NG	Martire *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	NG	Nagao & Takahashi (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	+	50	Anderson & Styles (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	NG	Simmon (1979a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	370	Baker & Bonin (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	NG	Brooks & Dean (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	50	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	–	NG	Anderson & Styles (1978)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	NG	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	370	Baker & Bonin (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	–	NG	Brooks & Dean (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation, fluctuation test	–	+	2	Gatehouse (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation, fluctuation test	+	+[c]	1	Hubbard *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Martire *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	5	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	185	Venitt & Crofton-Sleigh (1981)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	NT	NG	Simmon (1979a)
SAS, *Salmonella typhimurium* TA92, reverse mutation	+	+	NG	Brooks & Dean (1981)
ECW, *Escherichia coli* WP2 *uvrA*pKM101, reverse mutation	+	+	9	Matsushima *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvrA*pKM101, reverse mutation	+	+	NG	Venitt & Crofton-Sleigh (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	+	9	Matsushima *et al.* (1981)
EC2, *Escherichia coli* WP2B/r, reverse mutation	+	+	22	Matsushima *et al.* (1981)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation,	+	+	89	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe,* forward mutation	+	+	0.1	Loprieno (1981)
SCN, *Saccharomyces cerevisiae* D6, mitotic aneuploidy induction	+	+	25	Parry & Sharp (1981)
SCH, *Saccharomyces cerevisiae* D3, homozygosis by mitotic gene conversion	+	+	100	Simmon (1979b)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCH, *Saccharomyces cerevisiae* JD1, homozygosis by mitotic gene conversion	+	+	25	Sharp & Parry (1981)
SCH, *Saccharomyces cerevisiae* D7, homozygosis by mitotic gene conversion	+	+	14	Zimmermann & Scheel (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		720 ppm feed or inj	Kortselius (1979)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		2300 µg/mL inj	Vogel *et al.* (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		250 ppm feed	Woodruff *et al.* (1984)
DMH, *Drosophila melanogaster*, heritable translocation test	+		1800 ppm feed	Kortselius (1979)
DMH, *Drosophila melanogaster*, heritable translocation test	+		3000 ppm feed	Woodruff *et al.* (1984)
DIA, DNA damage (comet assay), male CBA mouse keratinocytes *in vitro*	+	NT	100	Yendle *et al*. (1997)
GCL, Gene mutation, Chinese hamster lung g 12 transgenic cells, *gpt* locus *in vitro*	+	NT	100	Klein & Rossman (1990)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro,* five different loci	+	NT	10	Gupta & Singh (1982)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	5	Nishi *et al.* (1984)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	50	Klein & Rossman (1990)
SIC, Sister chromatid exchange, Chinese hamster lung Don cells *in vitro*	+	NT	0.072	Abe & Sasaki (1977)
SIC, Sister chromatid exchange, Chinese hamster lung Don cells *in vitro*	+	NT	11.5	Baker *et al.* (1983)
SIC, Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	+	NT	5	Nishi *et al.* (1984)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster lung Don cells *in vitro*	+	NT	72	Abe & Sasaki (1977)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts *in vitro*	+	NT	30	Ishidate *et al*. (1988)
TBM, Cell transformation, BALB/c 3T3 'A31 clone' mouse cells	+	NT	1	Atchison *et al.* (1982)
TBM, Cell transformation, BALB/c 3T3 'A31 clone' mouse cells	+	NT	2.5	Baturay & Kennedy (1986)
TCM, Cell transformation, mouse C3H 10T½ cells *in vitro*	+	NT	18	Oshiro *et al.* (1981)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1535 in Swiss-Webster mice	+		405 po	Simmon *et al.* (1979)
GIH, Gene forward mutation, human fibroblasts (MIT-2 cells), *hprt* locus *in vitro*	+	NT	6.5	Penman *et al.* (1979)
GIH, Gene mutation, human fibroblasts, diphtheria toxin resistance (HF Dip^r) *in vitro*	+	NT	15	Gupta & Goldstein (1981)
TIH, Cell transformation, human foreskin epithelial cells	+	NT	7.5	Milo *et al.* (1981)
DVA, DNA strand breaks, Wistar rat liver *in vivo*	+		500 po × 1	Stewart (1981)
DVA, DNA strand breaks, male CBA mouse skin keratinocytes *in vivo*	+		800 µg/cm^2 skin × 1	Yendle *et al.* (1997)
GVA, Gene mutation, Muta™ Mouse stomach and liver *in vivo*	+		150 po × 1	Brault *et al.* (1996)
MVM, Micronucleus test, B6C3F$_1$ mouse bone marrow *in vivo*	?		~ 80 ip (80% LD_{50}) × 1	Salamone *et al.* (1981)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	–		46 ip × 2	Tsuchimoto & Matter (1981)
MVM, Micronucleus test, CD-1 mouse hepatocytes *in vivo*	+		27 ip × 2	Cliet *et al.* (1989)
MVM, Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	–		162 ip × 1	Cliet *et al.* (1993)
MVM, Micronucleus test, CD-1 mouse spermatids *in vivo*	+		54 ip × 1	Cliet *et al.* (1993)
MVM, Micronucleus test, CD-1 mouse splenocytes *in vivo*	+		53.7 ip × 1	Benning *et al.* (1994)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CBA, Chromosomal aberrations, Sprague-Dawley rat bone-marrow cells *in vivo*	(+)		100 iv × 1	Rees *et al.* (1979)
CBA, Chromosomal aberrations, Long-Evans rat bone-marrow cells *in vivo*	(+)		100 iv × 1	Rees *et al.* (1979)
COE, Chromosomal aberrations, C57BL/6J × CBA/Ca F_1 mouse oocytes *in vivo*	+		2 ip × 1	Santalo *et al.* (1987)
COE, Chromosomal aberrations, C57BL/6J × CBA/Ca F_1 mouse embryos *in vivo*	+		2 ip × 1	Santalo *et al.* (1987)
BID, Formation of DNA adducts *in vitro*	+	NT	2559	Chen *et al.* (1981)
BID, Formation of DNA adducts *in vitro*	+	NT	3603	Hemminki (1981)
BID, Formation of DNA adducts *in vitro*	+	NT	18 735	Randerath *et al.* (1981)
BVD, Binding (covalent) to DNA, STS mouse skin *in vivo*	+		~ 1150 μg/cm^2 skin	Colburn & Boutwell (1968)
BVP, Binding (covalent) to RNA and proteins, STS mouse skin *in vivo*	+		~ 1150 μg/cm^2 skin	Colburn & Boutwell (1968)
Apurinic/apyrimidinic site production in SV40 DNA *in vitro*	+	NT	2.0	Drinkwater *et al.* (1980)

[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; NG, not given; inj, injection; po, oral; ip, intraperitoneal; iv, intravenous; vap, vapour

[c] Freshly isolated rat hepatocytes used for metabolic activation

4.4.3 *Mechanistic considerations*

DNA from skin carcinomas and fibrosarcomas induced in mice by β-propiolactone was tested for its ability to transform NIH3T3 cells by DNA transfection. One of two squamous-cell carcinomas and one of three fibrosarcomas gave positive results in the transfection assay. The transformed phenotype of the positive transfectants was confirmed by the observation of anchorage-independent growth, tumorigenicity in nude mice and secondary transfection. One of the two β-propiolactone-induced squamous-cell skin carcinomas was found to contain an activated H-*ras* oncogene with an A→T transversion at the second nucleotide of codon 61. The mutation was detected in the NIH3T3 transfectant and in the original tumour. The mutation was not seen in the liver of the same animal. The A→T transversion mutation is consistent with a direct miscoding effect of a specific β-propiolactone–DNA adduct (Garte *et al.* 1985; Hochwalt *et al.* 1988).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The main use of β-propiolactone has been as an intermediate in the production of acrylic acid and its esters. It has also been used for the sterilization of vaccines and blood products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

β-Propiolactone was tested for carcinogenicity in mice by skin application and subcutaneous or intraperitoneal injection and in rats by inhalation exposure and subcutaneous injection, producing local tumours. The results obtained in studies in hamsters and guinea-pigs were equivocal.

5.4 Other relevant data

β-Propiolactone is a direct-acting alkylating agent. It forms DNA adducts. It is mutagenic in a wide variety of in-vitro and in-vivo systems, both in somatic and germ cells.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of β-propiolactone were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of β-propiolactone.

Overall evaluation

β-Propiolactone is *possibly carcinogenic to humans (Group 2B)*.

6. References

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