γ-BUTYROLACTONE

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

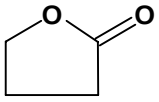
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 96-48-0

Chem. Abstr. Name: Dihydro-2(3-H)-furanone

Synonyms: γ-BL; 1,4-butanolide; butyric acid lactone; 4-butyrolactone

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_6O_2$ Relative molecular mass: 86.1

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Mercker & Kieczka, 1985; Budavari, 1996)

(*b*) *Boiling-point*: 204°C (Lide, 1997)

(*c*) *Melting-point*: –43.3°C (Lide, 1997)

(*d*) *Solubility*: Miscible with water, ethanol, diethyl ether, acetone and benzene (Lide, 1997)

(*e*) *Stability*: Stable at pH 7; rapidly hydrolysed by bases, slowly hydrolysed by acids (Weast, 1975)

(*f*) *Reactivity*: Reacts with inorganic acids and bases, alcohols and amines (Freifeld & Hort, 1967)

(*g*) *Conversion factor*: $mg/m^3 = 3.52 \times ppm$

1.2 Production and use

γ-Butyrolactone production in the United States in 1992 was estimated to be approximately 45 thousand tonnes per year (Datta, 1995). Information available in 1995 indicated that it was produced in six countries (Chemical Information Services, 1995).

γ-Butyrolactone is used principally as a chemical intermediate in the production of pyrrolidones, as an intermediate in organic synthesis, and as a solvent for many polymers (Mercker & Kieczka, 1985; Datta, 1995).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 27 000 workers in the United States were potentially exposed to γ-butyrolactone (see General Remarks). Occupational exposures may occur in its production, in the production of 2-pyrrolidone and related chemicals, and when it is used as a solvent.

1.3.2 *Environmental exposure*

γ-Butyrolactone has been found in alcoholic beverages, cooked meats, coffee, tomatoes and tobacco smoke (IARC, 1976; United States National Library of Medicine, 1998).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not recommended an 8-h time-weighted average threshold limit value for occupational exposures to γ-butyrolactone in workplace air.

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

2. Studies of Cancer in Humans

γ-Butyrolactone was one of the several agents evaluated in the case–control studies of soft-tissue sarcoma and non-Hodgkin lymphoma nested within the IARC international cohort of pesticide production workers and sprayers (Kogevinas *et al.*, 1995), which are described in the monograph on polychlorophenols in this volume. One case of soft-tissue sarcoma and one control were classified as exposed (odds ratio, 5.0; 95% confidence interval (CI), 0.3–80). Two cases of non-Hodgkin lymphoma and three controls were classified as exposed (odds ratio, 3.0; 95% CI, 0.5–18).

3. Studies of Cancer in Experimental Animals

γ-Butyrolactone was tested for carcinogenicity in mice by oral administration, subcutaneous injection and skin application and in rats by oral and subcutaneous administration. No carcinogenic effects were observed (IARC, 1976).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, eight to nine weeks of age, received γ-butyrolactone (purity, > 97%) in corn oil by gavage on five days per week for two years. The doses administered were 0, 262, and 525 mg/kg bw for both male and female

mice. The mean body weights of dosed male mice were lower than those of the controls throughout the study, but the differences in mean body weights decreased when male mice were housed individually at week 67. The final mean body weights of dosed male mice were 6% lower than that of the controls. Mean body weights of dosed female mice were also lower than those of the controls throughout the study, and the final mean body weights were from 14% to 17% lower than that of the controls. The survival in high-dose male mice was significantly lower than that of the controls (35/50, 30/50, 12/50) due to bite wounds and fighting in high-dose males recovering from the sedative effects of γ-butyrolactone. The survival of female dosed mice was similar to that of the controls (38/50, 34/50, 38/50). Increased incidences of proliferative lesions of the adrenal medulla in low-dose male mice were associated with γ-butyrolactone administration (phaeochromocytoma, benign or malignant: 2/48, 6/50, 1/50; hyperplasia: 2/48, 9/50, 4/50). The incidence of hepatocellular neoplasms in both dose groups of male mice was lower than the incidence in the controls (hepatocellular adenoma or carcinoma: 24/50, 8/50, 9/50). No increase in the incidence of tumours at other sites was observed in either sex (United States National Toxicology Program, 1992).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, eight to nine weeks of age, received γ-butyrolactone (purity, > 97%) in corn oil by gavage on five days per week for two years. The doses administered were 0, 112 and 225 mg/kg bw for male rats and 0, 225 and 450 mg/kg bw for female rats. The mean body weights of male rats given γ-butyrolactone were similar to those of the controls throughout the study. The mean body weight of high-dose females was 10–20% lower than that of the controls throughout the second year. The survival of high-dose male rats was slightly higher than that of the controls (control, 24/50; low-dose, 27/50; high-dose, 32/50) due primarily to a lower incidence of mononuclear cell leukaemia in the high-dose group (16/50, 15/50, 9/50). The survival of dosed females was similar to that of the controls (28/50, 27/50, 28/50). No increased incidence of neoplasms or non-neoplastic lesions in rats was reported (United States National Toxicology Program, 1992).

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*

γ-Butyrolactone rapidly hydrolyses in blood to γ-hydroxybutyric acid, which, when given to rats by inhalation, is mainly excreted as CO_2 (75–85% in 24 h) (IARC, 1976). The plasma half-life in rats of γ-butyrolactone after intravenous administration is less than one minute (Roth & Giarman, 1966, 1969).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

γ-Butyrolactone has relatively low toxicity, although sedative and hypnotic effects occur and bradycardia and coma can result from its ingestion (Higgins & Borron, 1996). These are likely to be due to its major metabolite, γ-hydroxybutyric acid, which is formed endogenously and found in low concentrations in the brain (Roth & Giarman, 1969; Borbély & Huston, 1972; Gold & Roth, 1977). γ-Butyrolactone did not sensitize guinea-pigs, following skin application (IARC, 1976).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of 10 pregnant rats received up to 500 mg/kg bw per day γ-butyrolactone by gavage on gestation days 6–15. No embryotoxicity was observed on day 21 of gestation (Kronevi *et al*., 1988).

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)

A large proportion of the genetic toxicity data on γ-butyrolactone is derived from a collaborative study involving up to seventeen laboratories.

γ-Butyrolactone does not induce DNA damage or mutations in bacteria, gene conversion or aneuploidy in yeast. Sex-linked recessive lethal mutations were not induced in *Drosophila melanogaster*. In cultured human cells, there was no indication of induction of gene mutations in one study. In contrast, sister chromatid exchanges and chromosomal aberrations were increased in one study with Chinese hamster ovary cells in the presence of an exogenous metabolic activation system, while chromosomal aberrations were not increased in another study in rat liver cells. Micronuclei were not induced in the bone-marrow cells of exposed mice in two studies.

Table 1. Genetic and related effects of γ-butyrolactone

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage, induction, SOS repair test, DNA strand breaks or cross-links	–	–	12 500	Thomson (1981)
ECL, *Escherichia coli pol A*/W3110-P3478, differential toxicity (liquid suspension test)	(+)	NT	NG	Rosenkranz *et al*. (1981)
ERD, *Escherichia coli rec* strains, differential toxicity	–	–	500	Green (1981)
ERD, *Escherichia coli rec* strains, differential toxicity	–	–	500	Ichinotsubo *et al*. (1981a)
ERD, *Escherichia coli rec* strains, differential toxicity	–	–	1000	Tweats (1981)
BRD, *Bacillus subtilis rec* strains, differential toxicity	–	+[c]	22 400 µg/disk	Kada (1981)
SAF, *Salmonella typhimurium* TM677, forward mutation, 8-azaguanine resistance	–	–	1000	Skopeck *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Baker & Bonin (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	–	–	500	Hubbard *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Ichinotsubo *et al*. (1981b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	5000	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Simmon & Shepherd (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	–	1250	Trueman (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Baker & Bonin (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation (fluctuation test)	–	–	500	Gatehouse (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	–	1250	Trueman (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Baker & Bonin (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (fluctuation test)	–	–	500	Gatehouse (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	MacDonald (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Rowland & Severn (1981)

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	–	–	NG	Simmon & Shepherd (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	NT	–	1250	Trueman (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Baker & Bonin (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	1250	Trueman (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Baker & Bonin (1981
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation (fluctuation test)	–	–	500	Gatehouse (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation (fluctuation test)	–	–	500	Hubbard *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Ichinotsubo *et al*. (1981b)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Rowland & Severn (1981)

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	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	–	1250	Trueman (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SAS, *Salmonella typhimurium* TA92, reverse mutation	–	–	1000	Brooks & Dean (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation (fluctuation test)	–	–	500	Gatehouse (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	NG	Matsushima *et al*. (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
ECR, *Escherichia coli* WP2 *uvrA*/pKM101, reverse mutation	–	–	NG	Matsushima *et al*. (1981)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	–	–	166	Jagannath *et al*. (1981)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	?[d]	NT	500	Sharp & Parry (1981a)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	–	2250	Zimmermann & Scheel (1981)
SCH, *Saccharomyces cerevisiae* 'race XII', homozygosis by mitotic recombination, ade2 locus	–	–	1000	Kassinova *et al*. (1981)
SCR, *Saccharomyces cerevisiae*, XV185-14C, reverse mutation	–	?	22	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	–	20	Loprieno (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	–	–	1000	Parry & Sharp (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		0.2% feed	Vogel *et al*. (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations (*y mei-9^{a} mei-41^{DS}*)	–		0.2% feed	Vogel *et al*. (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		28000 ppm feed	US National Toxicology Program (1992)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	1000	Perry & Thomson (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	+	3010	Loveday *et al*. (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	2580	Loveday *et al*. (1989)
CIR, Chromosomal aberrations, rat liver RL_1 cells *in vitro*	–	NT	250	Dean (1981)
GIH, Gene mutation, human fibroblast HSC172 cell line, diphtheria toxin resistance *in vitro*	–	–	500	Gupta & Goldstein (1981)
MVM, Micronucleus test, $B6C3F_1$ mouse bone-marrow cells *in vivo*	–		984 ip × 2	Salamone *et al*. (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	–		495 ip × 2	Tsuchimoto & Matter (1981)
SPM, Sperm morphology, (CBA × BALB/c)F_1 mice *in vivo*	–		560 ip × 5	Topham (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; NG, not given; ip, intraperitoneal
[c] S-9 from Japanese yellowtail fish
[d] Positive in dimethyl sulfoxide, negative in ethanol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to γ-butyrolactone may occur in its production and use as an intermediate and as a solvent. It has been detected in alcoholic beverages, tobacco smoke, coffee and several foodstuffs.

5.2 Human carcinogenicity data

No adequate data were available to the Working Group.

5.3 Animal carcinogenicity data

γ-Butyrolactone was tested for carcinogenicity in two studies in mice and two studies in rats by oral administration. It was also tested in mice by skin application in two studies and by subcutaneous injection in mice and rats in single studies. No carcinogenic effect was observed.

5.4 Other relevant data

γ-Butyrolactone rapidly hydrolyses in blood to γ-hydroxybutyric acid. γ-Butyrolactone has been extensively studied in in-vitro genetic toxicity tests in which the overwhelming majority of results did not indicate activity. Positive results were obtained in one study for chromosomal aberrations and sister chromatid exchanges in a Chinese hamster cell line. No mutagenic activity was observed *in vivo* in *Drosophila* or in mouse bone marrow micronucleus tests.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of γ-butyrolactone.

There is *evidence suggesting lack of carcinogenicity* of γ-butyrolactone in experimental animals.

Overall evaluation

γ-Butyrolactone is *not classifiable as to its carcinogenicity to humans* (Group 3).

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