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Toxicity

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**CAS Registry Number: 96-48-0**

### Names (NTP)

- Gamma-Butyrolactone
- 2(3h)-Furanone, Dihydro- (8ci)(9ci)

Selected toxicity information from HSDB, one of the National Library of Medicine's databases. <sup>1</sup>

### Human Toxicity Excerpts

- TOXIC BY INGESTION. [Sax, N.I. and R.J. Lewis, Sr. (eds.). Hawley's Condensed Chemical Dictionary. 11th ed. New York: Van Nostrand Reinhold Co., 1987., p. 193]\*\*PEER REVIEWED\*\*
- The usual symptoms include headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps, diarrhea, and discomfort in the chest. Signs include sweating, miosis, tearing, salivation and other excessive respiratory tract secretion, vomiting, cyanosis, papilledema, uncontrollable muscle twitches followed by muscular weakness, convulsions, coma, loss of reflexes, and loss of sphincter control. The last four signs are seen only in severe cases but do not preclude a favorable outcome if treatment is prompt and energetic. Cardiac arrhythmias, various degrees of heart block, and cardiac arrest may occur ... /Organic phosphorus pesticides/ [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 938]\*\*PEER REVIEWED\*\*

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### Non-Human Toxicity Excerpts

- ... 60 4-WK-OLD C3H MICE OF BOTH SEXES RECEIVED DIET CONTAINING 1000 MG GAMMA-BUTYROLACTONE/KG ... FOR LIFE ... IN C3H MICE, NO INCR IN INCIDENCES OF MAMMARY

- TUMORS IN FEMALES OR OF HEPATOMAS IN MALES WERE OBSERVED COMPARED WITH THOSE IN 54 MALE & 61 FEMALE UNTREATED CONTROLS. [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 234 (1976)]\*\*PEER REVIEWED\*\*
- OF 34 NEWBORN XVII/G MICE GIVEN SC INJECTIONS OF 1 UG... ON 1ST, 4TH & 8TH DAYS OF LIFE, 18 (53%) DEVELOPED LUNG TUMORS (AVG SURVIVAL, 590 DAYS) COMPARED WITH 27/44 (61%) UNTREATED CONTROLS (AVG SURVIVAL, 595 DAYS). [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 235 (1976)]\*\*PEER REVIEWED\*\*
  - NO LOCAL TUMORS WERE OBSERVED IN ... 16 FEMALE SWISS-WEBSTER MICE GIVEN 12 SC INJECTIONS OF 0.005 MG ... IN 0.1 ML TRICAPRYLIN THRICE WEEKLY FOR 4 WK; 11 MICE SURVIVED 18 MO. [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 235 (1976)]\*\*PEER REVIEWED\*\*
  - NO INCR IN TUMOR INCIDENCE WAS OBSERVED IN GROUP OF 30 FEMALE SWISS ICR/HA MICE PAINTED WITH 0.1 ML OF 10% SOLN IN ACETONE THRICE WEEKLY FOR LIFE; MEAN SURVIVAL TIME WAS 495 DAYS. [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 235 (1976)]\*\*PEER REVIEWED\*\*
  - GAMMA-BUTYROLACTONE ADMIN DERMALLY, 10 MG, 3X WEEKLY FOR 292 DAYS TO ICR/HA MICE, PRODUCED 2/30 PAPILOMAS. CONSIDERED NEGATIVE. /FROM TABLE/ [Searle, C. E. (ed.). Chemical Carcinogens. ACS Monograph 173. Washington, DC: American Chemical Society, 1976., p. 190]\*\*PEER REVIEWED\*\*
  - SYMPTOMS /IN RAT & MOUSE/ WERE THOSE OF WEAKNESS, UNCONSCIOUSNESS, & INCR DEPTH OF RESPIRATION. IT APPEARS TO BE READILY ABSORBED THROUGH GUINEA PIG SKIN WITH SOME IRRITATION PRODUCED. [Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963., p. 1825]\*\*PEER REVIEWED\*\*
  - GAMMA-BUTYROLACTONE HAS ANESTHETIC PROPERTIES ... . [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 236 (1976)]\*\*PEER REVIEWED\*\*
  - ANESTHETIC DOSES OF GAMMA-BUTYROLACTONE, WHICH PRODUCE HYPERTHERMIA IN RATS, INCR INITIAL POSITIVITY OF CLICK-EVOKED CORTICAL POTENTIALS. GAMMA-BUTYROLACTONE (400 MG/KG IP) & ITS METABOLITE, GAMMA-HYDROXYBUTYRIC ACID (750 MG/KG IP) DEPRESSED RESPIRATION. [BORBELY AA ET AL; SLEEP, PROC EUR CONGR, 1ST 355 (1973)]\*\*PEER REVIEWED\*\*
  - IN NORMOXIC RATS GAMMA-BUTYROLACTONE CAUSED MILD METABOLIC ACIDOSIS, AS EVIDENCED BY DECR ARTERIAL PH & HCO<sub>3</sub>-CONTENT. IN HYPOXIC ANIMALS GAMMA-BUTYROLACTONE HAD NO EFFECT. [MACMILLAN V; BRAIN RES 146 (1): 177 (1978)]\*\*PEER REVIEWED\*\*
  - GAMMA-BUTYROLACTONE (75, 150, 300, & 600 MG/KG, IV) CAUSED DOSE-DEPENDENT CHANGES IN LEVEL OF

- CONSCIOUSNESS, EEG ACTIVITY, & RATE OF LOCAL CEREBRAL GLUCOSE UTILIZATION IN RATS. [WOLFSON LI ET AL; J NEUROCHEM 29 (5): 777 (1977)]\*\*PEER REVIEWED\*\*
- @ 600 MG/KG IV IN RATS LOCAL CEREBRAL GLUCOSE UTILIZATION WAS DEPRESSED TO 32 & 58% OF CONTROLS IN GRAY & WHITE MATTER; ALL 26 GRAY STRUCTURES STUDIED SHOWED SIMILAR DOSE-RESPONSE RELATIONS. GAMMA-BUTYROLACTONE DEPRESSED CEREBRAL ENERGY METAB THROUGHOUT BRAIN. [WOLFSON LI ET AL; J NEUROCHEM 29 (5): 777 (1977)]\*\*PEER REVIEWED\*\*
  - LOW DOSES OF GAMMA-BUTYROLACTONE (100 & 200 MG/KG) HAD A BIPHASIC EFFECT ON ACTIVITY. INITIALLY, THE ACTIVITY OF RATS WAS REDUCED, & THIS REDUCTION WAS THEN FOLLOWED BY A PERIOD OF HYPERACTIVITY. THE INCREASE IN ACTIVITY COULD BE DUE TO A RELEASE OF DOPAMINE. [DAVIES JA; PSYCHOPHARMACOL (BERLIN) 60 (1): 67 (1978)]\*\*PEER REVIEWED\*\*
  - IV ADMIN OF 100 MG GAMMA-BUTYROLACTONE PER KG ELEVATED BLOOD PRESSURE & STIMULATED RESPIRATION IN ANESTHETIZED DOGS, BUT HAD OPPOSITE EFFECTS IN ANESTHETIZED CATS. [HAMPEL H, HAPKE HJ; ARCH INT PHARMACODYN THER 171 (2): 306 (1968)]\*\*PEER REVIEWED\*\*
  - The teratogenic potential of gamma-butyrolactone was studied in rats. Pregnant Sprague-Dawley rats were given 0, 10, 50, 125, 250, or 500 mg/kg gamma-butyrolactone by gavage on days six through 15 of gestation. Each female was observed for signs of intoxication. Body weights were measured daily from days zero through 21 of gestation, and food and water consumption were monitored at 3 day intervals. On day 21, dams were killed and the uteri were removed. The position and number of fetuses in-utero, the number of dead and live fetuses, and fetal and placental weights were recorded. Fetuses were examined for malformations, and dams were necropsied. Four dams, three in the 50 mg/kg group and one in the 125 mg/kg group, died during treatment. Necropsy showed lung edema, hyperemia, and emphysema. Gamma-butyrolactone did not affect maternal body weight or feed and water consumption. Placental weights were significantly reduced in treated animals at all doses. Mean fetal weights were significantly increased in the 50, 125, and 250 mg/kg groups. No other treatment related changes of significance were seen either in the dams or fetuses. Some minor skeletal alterations seen in fetuses did not appear systematically and were not attributed to gamma-butyrolactone. /It was/ noted that the apparent relationship between gamma-butyrolactone exposure and increased fetal weight cannot be explained. [Kronevi T et al; Pharmacol & Toxicol 62 (1): 57-8 (1988)]\*\*PEER REVIEWED\*\*
  - ... Conclusions: Under the conditions of these 2 yr gavage studies, there was no evidence of carcinogenic activity of gamma-butyrolactone in male F344/N rats given 112 or 225 mg/kg or in female F344/N rats given 225 or 450 mg/kg in corn oil. There was equivocal evidence of carcinogenic activity of gamma-butyrolactone in male B6C3F1 mice based on marginally increased incidences of adrenal medulla pheochromocytomas and hyperplasia in the low-dose group. The sensitivity of the study in male mice to detect a carcinogenic effect was reduced by the low survival of the high dose group associated with fighting. There was no evidence of carcinogenic activity of gamma-butyrolactone in female B6C3F1 mice given 262 or 525 mg/kg in corn oil. [Toxicology & Carcinogenesis Studies of gamma-Butyrolactone in F344/N Rats and B6C3F1 Mice (Gavage Studies). Technical Report Series No. 406 (1992) NIH Publication No. 92-3137 U. S. Department of Health and Human Services, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709]\*\*PEER REVIEWED\*\*

- gamma-Butyrolactone is an oily liquid, with a melting point of - 44 xC and boiling point of 206 xC. It is used as chemical intermediate, as solvent for polymers, in paint removers, and in drilling oil. gamma-Butyrolactone appears to be readily absorbed through guinea pig skin. In rat, at least 10% of the applied dose penetrated the skin. Data describing the uptake of gamma-butyrolactone from the gastro-intestinal or the respiratory system were not located in the literature. The biological degradation of gamma-butyrolactone in mammals is rapid. It is hydrolysed to gamma-hydroxybutyric acid in the blood and liver. In rats, gamma-hydroxybutyric acid is excreted as CO<sub>2</sub>. gamma-Butyrolactone has a weak narcotic effect due to its fast metabolic conversion to gamma-hydroxybutyric acid, which has an effect on the central nervous system. gamma-Butyrolactone has a moderate, acute oral toxicity. The oral LD<sub>50</sub> of gamma-butyrolactone is in the range of 1540 - 1 800 mg/kg in rat, 800 - 1720 mg/kg in mouse, and 500 - 1 690 mg/kg in guinea pig. The symptoms are weakness, unconsciousness, and increased depth of respiration. Rats given more than 700 mg/kg gamma-butyrolactone intragastrically died within a few days of respiratory failure and lung congestion. In Scandinavia some cases of poisoning in children have been reported after ingestion of small amounts (less than 8 ml) of gamma-butyrolactone. The LD<sub>50</sub> by skin contact is greater than 5 000 mg/kg. Limited inhalation data from acute exposure were available. In rats, inhalation of a saturated atmosphere (8 hours at 20 xC) indicated a low acute toxic effect of gamma-butyrolactone. gamma-Butyrolactone appears to produce some skin irritation when applied dermally to guinea pigs but not to rabbits. In an experimental study on 200 human volunteers, no primary irritative effect of undiluted y-butyrolactone was found, and there were no indications of a sensitizing action on the skin. Severe irritative effects on the rabbit eye have been reported following instillation of gamma-butyrolactone in the conjunctival sac. The literature offers no evidence of gamma-butyrolactone causing toxic effects following repeated exposure. Doses of 100 - 400 mg/kg were well tolerated and could be given repeatedly by gavage to rats for over 7 months. In a 90-day feeding study with beagles receiving up to 0.8% gamma-butyrolactone in the feed, no symptoms of intoxication or pathological effects were noted. However, a dose of approximately 3 000 mg/kg per day of gamma-butyrolactone in the drinking water to male Sprague-Dawley rats over a period of 4 weeks caused a slight, but significant reduction in weight gain. gamma-Butyrolactone has been tested for genotoxicity in several short-term tests, and discordant results were obtained. A positive response in some of the in vitro assays (sister chromatid exchange, chromosome aberration, and cell transformation) seems to be dependent on addition of an exogenous metabolism system. gamma-Butyrolactone was negative in the UDS, bacterial mutagenicity tests, tests with yeast (mitotic crossing over, mitotic gene conversion, mitotic aneuploidy), and in vivo tests (*Drosophila* recessive lethals, micronucleus test in mice, and abnormal spermatozoa). gamma-Butyrolactone, given orally (500 - 1000 mg/kg/day) to male rats was shown to reduce gonadal development resulting in significant reduced testicular weights. Foetal weight was significant increased in female rats gavaged with 50, 125, and 250 mg/kg of y-butyrolactone on days 6 to 15 of pregnancy. No differences from unexposed animals in the corpora lutea, total implantations, ratio of dead to live fetuses, resorptions, and pre- and post-implantation losses were noted at doses up to 1000 mg/kg. Furthermore, there were no visceral or skeletal malformations due to gamma-butyrolactone exposure. Doses of 500 - 750 mg/kg given intraperitoneally blocked ovulation in Sprague-Dawley rats. A reduction in the number of rats ovulating was evident at 62.5 mg gamma-butyrolactone/kg. gamma-Butyrolactone was tested for carcinogenicity

in mice by oral administration, subcutaneous injection or by skin application, and in rats by subcutaneous administration. All the tests were negative; however, several reports are inadequately documented. From a long-term oral study in rats and mice, there was no evidence of carcinogenic activity of gamma-butyrolactone in rats. There was equivocal evidence of carcinogenic activity of gamma-butyrolactone in male mice (the sensitivity of this part of the study was, however, reduced by a low survival of the high-dose group). There was no evidence of carcinogenic activity of gamma-butyrolactone to female mice. Thus, there is no evidence of carcinogenic effect of gamma-butyrolactone in animals and no data from humans. The critical effects for gamma-butyrolactone appears to be a weak narcotic effect, a moderate, acute oral toxicity, and eye irritation. An effect of gamma-butyrolactone reproduction can not be excluded. [Larsen J, S derlund E; Nord 29: 25-48 (1993)]\*\*PEER REVIEWED\*\*

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## Human Toxicity Values

- None found

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## Non-Human Toxicity Values

- LD50 MOUSE IV 880 MG/KG [HAMPEL H, HAPKE HJ; ARCH INT PHARMACODYN THER 171 (2): 306 (1968)]\*\*PEER REVIEWED\*\*
- LD50 MOUSE IP 880 MG/KG [HAMPEL H, HAPKE HJ; ARCH INT PHARMACODYN THER 171 (2): 306 (1968)]\*\*PEER REVIEWED\*\*
- LD50 MOUSE ORAL 1260 MG/KG [HAMPEL H, HAPKE HJ; ARCH INT PHARMACODYN THER 171 (2): 306 (1968)]\*\*PEER REVIEWED\*\*
- LD50 Rat oral 17.2 ml/kg [Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 243]\*\*PEER REVIEWED\*\*
- LD50 Rat oral 1540 mg/kg [Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 545]\*\*PEER REVIEWED\*\*
- LD50 Rat ip 1000 mg/kg [Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 545]\*\*PEER REVIEWED\*\*
- LD50 Mouse oral 1720 mg/kg [Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 545]\*\*PEER REVIEWED\*\*
- LD50 Mouse ip 1100 mg/kg [Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 545]\*\*PEER REVIEWED\*\*
- LD50 Mouse oral 9.0 ml/kg [Clayton, G.D., F.E. Clayton (eds.) Patty's Industrial Hygiene and Toxicology. Volumes 2A, 2B, 2C, 2D, 2E, 2F: Toxicology. 4th ed. New York, NY: John Wiley & Sons Inc., 1993-1994., p. 4693]\*\*PEER REVIEWED\*\*

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## Absorption, Distribution and Excretion

- GAMMA BUTYROLACTONE ... IS ... RAPIDLY HYDROLYSED TO GAMMA HYDROXYBUTYRIC ACID ... IN RATS, (1-(14)C)- OR (4-(14)C)-HYDROXYBUTYRATE GIVEN BY INHALATION IS EXCRETED AS (14)CO<sub>2</sub>; ABOUT 66% OF ACTIVITY WAS EXCRETED IN 6 HR & ADDNL 10-20% WITHIN 18 HR. [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 236]\*\*PEER REVIEWED\*\*

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## Metabolism/Metabolites

- ... AFTER IV ADMIN TO RATS IT IS CONVERTED RAPIDLY INTO GAMMA-HYDROXYBUTYRIC ACID WHICH CAUSES DEPRESSION OF CNS. IT IS ALSO RAPIDLY HYDROLYZED TO GAMMA-HYDROXYBUTYRIC ACID IN BLOOD & LIVER. [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work)., p. V11 236]\*\*PEER REVIEWED\*\*

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## TSCA Test Submissions

- gamma-Butyrolactone (CAS # 96-48-0) was evaluated for acute inhalation toxicity in Sprague-Dawley rats (5/sex) exposed under dynamic conditions to a mean concentration of 5.1 (range, 4.8-5.3) mg/L in air for 4 hours. Eighty-three percent of particles measured 10 microns or less and ambient gamma-butyrolactone levels were tested 4 times during approximate 1-hour intervals. No control group was tested; quantitative evaluations were based on baseline data. No deaths occurred throughout treatment or 14-day post-exposure observation. Immediately following exposures, rats exhibited pharmacotoxic signs including prostration, lethargy, shallow breathing, limb disuse, and clear discharge from the nose. All animals were hyperactive on Day 2. By Day 7 and again at Day 14, no signs of toxicity remained, save progressive weight loss from Day 2 post-exposure. No treatment-related pathology was identified upon terminal necropsy.[Monsanto Co; Acute Toxicity of Gamma-Butyrolactone Administered by Inhalation to Sprague-Dawley Male and Female Rats (Final Report); 05/02/86; EPA Document No. 88-920000078; Fiche No. OTS0534527]\*\*UNREVIEWED\*\*
- Clastogenic activity was evaluated in 3 cultures of RL1 rat liver cells per dose, exposed for 22 hours to gamma-butyrolactone at concentrations of 0, 62.5, 125.0, or 250.0 ug/ml of culture medium. Concentrations were chosen to be approximately 1/4, 1/2, and 1x the GI50 (concentration at which 50% growth inhibition is achieved). Both positive (7,12-dimethylbenzanthracene) and solvent (dimethylsulfoxide) controls were used. No metabolic activation system was used. Cell division was arrested, and at least 280 metaphases from each test concentration were examined. Neither chromosomal nor chromatid aberrations were significantly increased at any test concentration. The proportions of cells showing chromatid aberrations was 0.0%, 0.0%, 0.9%, and 1.1% at 0.0, 62.5, 125.0, and 250.0 ug/ml, respectively. No cells showed chromosomal aberrations. Although the positive control showed 4.6% of cells with chromatid aberrations, no chromosomal aberrations were induced.[Shell Chem. Co.; The Activity of 27 Coded Compounds in the

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## Footnotes

<sup>1</sup> Source: the [National Library of Medicine's Hazardous Substance Database](#), 02/28/2006.

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