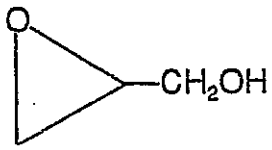
GLYCIDOL

CAS: 556-52-5

2,3-Epoxy-1-propanol; Epoxypropyl alcohol; Glycide

$C_3H_6O_2$



TLV–TWA, 2 ppm (6.1 mg/m^3)

A3 — Animal Carcinogen

1961: TLV–TWA, 50 ppm, proposed

1962–1980: TLV–TWA, 50 ppm

1976–1980: TLV–STEL, 75 ppm

1979: TLV–TWA, 25 ppm; TLV–STEL, 100 ppm; proposed

1981–1986: TLV–STEL, 100 ppm

1981–1995: TLV–TWA, 25 ppm

1987: TLV–STEL deleted

1995: TLV–TWA, 2 ppm; A3, Animal Carcinogen; proposed

1996: TLV–TWA, 2 ppm; A3

1996: Documentation revised

Chemical and Physical Properties

Glycidol is a colorless, viscous, combustible liquid. Chemical and physical properties include:

Molecular weight: 74.08
Specific gravity: 1.12
Melting point: –45°C
Boiling point: 166.11°C at 760 torr (decomposes)
Vapor pressure: 0.9 torr at 25°C
Saturated air concentration: 1180 ppm at 25°C
Flash point: 72.22°C, closed cup
Conversion factors: 1 ppm = 3.03 mg/m^3;
1 mg/m^3 = 0.33 ppm
Solubility: soluble in water and organic solvents

Major Uses or Sources of Occupational Exposure

The primary use for glycidol is as a stabilizer in the manufacture of vinyl polymers. It is also used as an intermediate in the production of pharmaceuticals, as an additive for oil and synthetic hydraulic fluids, and as a diluent in some epoxy resins. There is perhaps only one site of glycidol manufacture in the United States. In a total of 54 industrial hygiene air monitoring samples over 14 years, no exposures were found to be in excess of 2 ppm.[1]

Animal Studies

Acute

Hine et al.[2] found that glycidol was irritating to the lungs of mice and rats, with pneumonitis and emphysema being the usual findings following vapor exposure. A 4-hour LC_{50} was reported as 450 ppm in mice, while an 8-hour LC_{50} was 580 ppm in rats. Glycidol is poorly absorbed through the skin; the dermal LD_{50} for a 7-hour exposure of rabbits was 1980 mg/kg with only minimal signs of systemic toxicity noted. Dermal contact with glycidol was considered only moderately irritating to rabbit skin after a single application; repeated applications, however, caused severe irritation after 4 days. Application of a drop of pure glycidol to the eye of rabbits caused severe, but reversible, corneal injury.

Subchronic

Rats repeatedly exposed to glycidol in air at 400 ppm for 50 daily 7-hour exposures (except weekends) showed very slight irritation of the eyes, with slight lacrimation and encrustation of the eyelids, and slight respiratory distress following the first few exposures. These signs did not increase in severity with subsequent exposures. Except for a slight retardation in body weight gain when compared with concurrent controls, no evidence of cumulative toxicity could be detected. Necropsy at conclusion of the 50 daily exposures disclosed no gross lesions and only a slight decrease in the amount of peritoneal fat. No treatment-related histopathologic changes were reported.[2]

Glycidol (94% pure) was administered in water by gavage to groups of Fischer 344/N rats and B6C3F1 mice of each sex for 16 days or 13 weeks.[3] In the 16-day studies, glycidol doses for groups of five rats or five mice of each sex ranged from 37.5 to 600 mg/kg; vehicle controls received distilled water. All rats receiving 600 mg/kg died between days 3 and 13. Edema and degeneration of the epididymal stroma, atrophy of the testes, and granulomatous inflammation of the epididymis occurred in males receiving 300 mg/kg. All mice receiving 600 mg/kg and two males and two females receiving 300 mg/kg died by day 4 of the study. Focal demyelination in the medulla and thalamus of the brain occurred in all females receiving 300 mg/kg.

In the 13-week studies,[3] groups of ten rats and mice were dosed at 25 to 400 mg/kg, 5 days/week and 19 to 300 mg/kg, 5 days/week, of glycidol, respectively; vehicle controls received distilled water. All rats receiving 400 mg/kg died by the second week of the study, and three males and one female receiving 200 mg/kg died during weeks 11 to 12 of the study. Sperm count and sperm motility were reduced in rats receiving 100 or 200 mg/kg. Necrosis of the cerebellum, demyelination in the medulla of the brain, tubular degeneration and/or necrosis of the kidney, lymphoid necrosis of the thymus, and testicular

atrophy and/or degeneration occurred in rats receiving 400 mg/kg. All mice that received 300 mg/kg died by week 2 of the study; mice receiving 150 mg/kg died during weeks 4 to 8 for males and weeks 1 to 5 for females. Sperm count and sperm motility were reduced in glycidol-treated mice. Compound-related histopathologic lesions included demyelination of the brain in males and females that received 150 or 300 mg/kg, testicular atrophy at all doses, and renal tubular cell degeneration in male mice receiving 300 mg/kg.

Additional studies to evaluate neurotoxic threshold are currently planned.[1]

Chronic/Carcinogenicity

In a study to determine the potential dermal carcinogenicity of glycidol, 20 female ICR/Ha Swiss mice were topically administered 100 mg of a 5% solution of glycidol in acetone three times weekly for 520 days. No tumors of any type resulted.[4]

Gavage dosing with glycidol at 37.5 or 75 mg/kg (rats) or 25 or 50 mg/kg (mice), 5 days/week for 2 years induced a dose-related increase in the numbers of neoplastic changes in tissues.[3] Many animals with neoplasms were sacrificed in a moribund condition, and virtually all (196/200) exposed rats died before the end of the 2-year study. The most prominent lesion in male rats was mesothelioma, arising in the tunica vaginalis with frequent metastasis into the peritoneal cavity. Mesotheliomas occurred in 3/49 of the vehicle controls, 34/50 of the low-dose (38 mg/kg), and 39/47 of high-dose (75 mg/kg) male rats. Neoplasms of the mammary gland were prominent in female rats. The combined incidences of fibroadenomas and adenocarcinomas were 14/50 in vehicle control, 34/48 in the low-dose, and 37/48 in high-dose female rats. The dose-related increases in the incidences of neoplasms of the mammary gland, brain, thyroid gland, and forestomach in male and female rats; of the tunica vaginalis/peritoneum, skin, intestine, and zymbal gland in males; and of the oral mucosa, clitoral gland, and hematopoietic system (mononuclear cell leukemia) in females were considered by the National Toxicology Program (NTP)[3] to be clear evidence of the carcinogenic activity of glycidol in F344/N rats.

Harderian gland neoplasms were increased in mice of each sex exposed to glycidol.[3] The incidences of adenomas or adenocarcinomas (combined) were 8/46 in vehicle control, 12/41 in male mice given 25 mg/kg/day, and 22/44 in the male mice given 50 mg/kg/day and were 4/46 in vehicle control, 11/43 in low-dose, and 17/43 in high-dose female mice. The incidences of adenomas, fibroadenomas, or adenocarcinomas (combined) of the mammary gland in female mice were markedly increased, occurring in 2/50 of vehicle controls, 6/50 of low-dose, and 15/50 of high-dose female mice. In addition, forestomach, liver, and lung neoplastic lesions were increased in male mice, and neoplasms of the uterus and subcutaneous tissue were increased in female mice. The dose-related increase in the incidence of neoplasms in each of these tissues was considered clear evidence by the NTP of the carcinogenicity of glycidol in mice.[3]

Chemical-related non-neoplastic lesions in both rats and mice exposed to glycidol included hyperkeratosis and epithelial dysplasia of the forestomach. Fibrosis of the spleen was also present in rats of each sex, and cysts of the preputial gland and kidney were present in male mice.

Reproductive/Developmental

Testicular atrophy was observed in rats that received 300 or 400 mg/kg of glycidol in 16-day or 13-week oral intubation studies and in mice receiving 19, 38, 75, 150, or 300 mg/kg for 13 weeks.[3] Sperm count and sperm motility were reduced in male rats that received 100 or 200 mg/kg and in male mice that received 19, 38, 75, 150, or 300 mg/kg daily.

The teratogenic potential of glycidol has been evaluated in both rats and mice. Intra-amniotic injection of glycidol into pregnant Sprague–Dawley rats on day 13 of gestation caused embryolethality and induced malformations in a significant number of fetuses;[5] however, the parenteral route of administration and the practice of placing a high, local xenobiotic concentration directly into the embryo precludes use of these data in human health risk assessment. No evidence of teratogenicity was observed in a study in which pregnant CD-1 mice received 100, 150, or 200 mg/kg glycidol by gavage during days 6 to 15 of gestation.[6]

Genotoxicity Studies

Glycidol induced mutations in *Salmonella typhimurium* both with and without S9 activation.[3,7–12] Glycidol has also induced gene mutations in *Saccharomyces cerevisiae*,[13] *Schizosaccharomyces pombe*,[14,15] and *Neurospora crossa*[16] in the absence of exogenous activation. Glycidol was positive in the absence of exogenous metabolic activation in the mouse lymphoma assay[3,10] and induced unscheduled DNA synthesis in human W138 cells.[10]

In cytogenetic tests with Chinese hamster ovary (CHO) cells and human lymphocytes, addition of glycidol to the media was associated with an increased number of sister-chromatid exchanges and chromosomal aberrations in the absence of S9.[3,17] Glycidol administration induced sex-linked recessive lethal mutations and reciprocal translocations in the germ cells of male *Drosophila melanogaster* exposed by feeding.[3] The incidence of chromosomal aberrations was increased in the bone marrow of male B6C3F1 and male and female Wistar rats administered glycidol by intraperitoneal injection.[3,18]

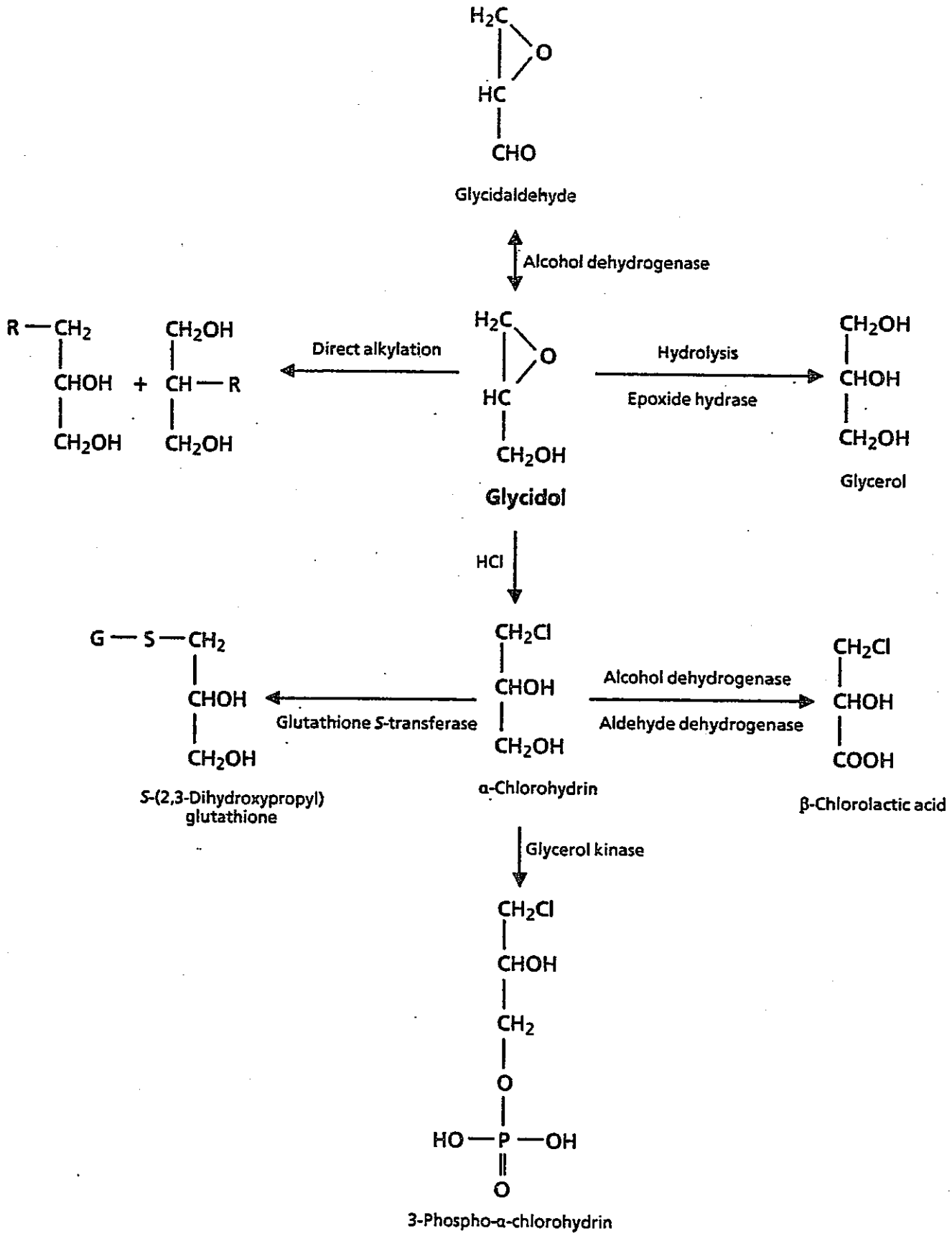


Figure 1. Metabolic Pathways for Glycidol [Reproduced with permission from reference 3.]

Pharmacokinetic/Metabolism Studies

The major urinary metabolites isolated from rats administered glycidol by intraperitoneal injection were S-(2,3-dihydroxypropyl) glutathione, S-(2,3-dihydroxypropyl) cysteine, and beta-chlorolactic acid (Figure 1).[3] The latter compound was identified as the only radioactive urinary metabolite of glycidol isolated from rats administered [^{36}Cl] saline for 3 days before glycidol administration.[19] The same urinary metabolites were found after -chlorohydrin administration, suggesting that glycidol was converted to -chlorohydrin by direct reaction with hydrochloric acid in the stomach. Alpha-chlorohydrin may then be converted to the glutathione metabolite by glutathione transferase or oxidized to -chlorolacetate by the successive action of alcohol and aldehyde dehydrogenases. The conversion of glycidol to glycerol has been observed in rat liver microsomal preparations.[20]

Human Studies

Only one piece of information was identified relating to workplace exposure to glycidol in which the sole domestic manufacturer of glycidol related industrial hygiene results conducted at all customer sites. These studies indicated that about 70 persons were exposed annually at concentrations not exceeding 2 ppm. No adverse effects on worker health were reported.[21]

TLV Recommendation

Glycidol is an ocular, upper respiratory tract, and skin irritant: at high concentrations, it causes narcosis in animals. Minimal effects were observed in rats from repeated exposure to glycidol at 400 ppm, and acute exposures provided a mouse 4-hour LC_{50} of 450 ppm and a rat 8-hour LC_{50} of 580 ppm.[2] In view of the carcinogenic activity of glycidol[3] and its genotoxic potential, a TLV–TWA of 2 ppm is proposed. No adverse effects have been recorded in routine physical examinations of workers exposed routinely to this concentration.[21] At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. Given the clear evidence for glycidol carcinogenicity in rodents given oral glycidol in lifetime studies,[3] the A3, Animal Carcinogen, designation is warranted. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL–TWA of 25 ppm for glycidol. OSHA concluded that this limit would protect workers against the significant risk of eye, respiratory, and pulmonary irritation potentially associated with exposure to this substance.[22] As a result of the Eleventh Circuit Court of Appeals decision in 1992 in the case of AFL and CIO vs. OSHA Department of Labor, 965 F.2d 962, the current PEL is 50 ppm.[23] The 1989 OSHA PEL was consistent with the presently adopted ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL–TWA of 25 ppm by concurrence with the 1989 OSHA PEL for glycidol.[22] NIOSH has established an IDLH value of 500 ppm for this substance.

ACGIH Rationale for TLVs that Differ from the PEL or REL: The consistent genotoxicity and significant carcinogenic activity of glycidol evidenced in animal studies at sites distant from initial contact warrant a reduction of the TLV and classification as an Animal Carcinogen.

NTP Studies: NTP administered glycidol by gavage to rats at doses of 0, 38, or 75 mg/kg and to mice at doses of 0, 25, or 50 mg/kg. Clear evidence of carcinogenic activity was found in male and female rats and in male and female mice. A chemical disposition study of glycidol has been planned by NTP. Glycidol was positive in the *Salmonella* and mouse lymphoma assays, in the *Drosophila* tests for sex-linked recessive lethal mutations and reciprocal translocation, and in cultured CHO cells for the induction of chromosomal aberrations and sister-chromatid exchanges.

Other Nations

Australia: 25 ppm (1990); Federal Republic of Germany: 50 ppm, short-term momentary level 100 ppm, 5 minutes, 8 times per shift (1995).

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