GLYCIDOL

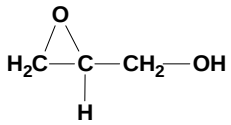
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 556-52-5
Deleted CAS Reg. Nos: 61915-27-3; 98913-54-3
Chem. Abstr. Name: Oxiranemethanol
IUPAC Systematic Name: 2,3-Epoxypropan-1-ol
Synonyms: Allyl alcohol oxide; epihydrin alcohol; 1,2-epoxy-3-hydroxypropane; 2,3-epoxy-1-propanol; (±)-2,3-epoxy-1-propanol; glycide; (±)-glycidol; (RS)-glycidol; dl-glycidol; glycidyl alcohol; hydroxy-1,2-epoxypropane; 1-hydroxy-2,3-epoxypropane; 2-(hydroxymethyl)oxirane; 3-hydroxypropylene oxide; oxiranyl-methanol; racemic glycidol

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_3H_6O_2$ Relative molecular mass: 74.08

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless, odourless liquid (Sienel *et al*., 1987)
(*b*) *Boiling-point*: 162 °C (decomposes) (Verschueren, 1996)
(*c*) *Melting-point*: –54 °C (Verschueren, 1996)
(*d*) *Density*: 1.143 g/cm^3 at 25 °C (Lide & Milne, 1996)
(*e*) *Spectroscopy data*: Infrared (prism [15765]; grating [28381]), nuclear magnetic resonance (proton [18790]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996)

(*f*) *Solubility*: Miscible in all proportions in water, alcohols, ketones, esters, ethers and aromatics; almost insoluble in aliphatic hydrocarbons (Sienel *et al*., 1987)
(*g*) *Volatility*: Vapour pressure, 120 Pa at 25 °C (American Conference of Governmental Industrial Hygienists, 1999); relative vapour density (air = 1), 2.15 (Verschueren, 1996)
(*h*) *Stability*: Flash-point, 71 °C (Sienel *et al*., 1987); reacts vigorously with strong caustic soda, strong sulfuric acid and with anhydrous metal halides, such as stannic and ferric chlorides (Dixie Chemical Co., 1995)
(*i*) *Octanol/water partition coefficient (P)*: log P, –0.95 (Hansch *et al.*, 1995)
(*j*) *Conversion factor*[1]: $mg/m^3 = 3.03 \times ppm$

1.1.4 *Technical products and impurities*

Glycidol is commercially available with a minimum purity of 95% and a maximum water content of 1% (Dixie Chemical Co., 1999).

Trade names for glycidol include: Epiol OH.

1.1.5 *Analysis*

Glycidol can be determined in workplace air by adsorbing the air sample on charcoal, desorbing with tetrahydrofuran and analysing by gas chromatography with flame ionization detection (Eller, 1994).

1.2 Production

Glycidol is commercially produced by two methods: (1) epoxidation of allyl alcohol with hydrogen peroxide and a catalyst (tungsten or vanadium); and (2) reaction of epichlorohydrin with caustic (Grigor'ev *et al.*, 1979; Yoshida & Koyama, 1992; Richey, 1993; Hutchings *et al.*, 1995).

Information available in 1999 indicated that glycidol was manufactured by two companies in Japan, and one company each in Germany and the United States (Chemical Information Services, 1999).

1.3 Use

In 1956, glycidol was only used for research purposes (Hine *et al*., 1956), but by 1978 it was used in the preparation of glycerol, glycidyl ethers, esters and amines in the pharmaceutical industry (Proctor & Hughes, 1978) and as a sterilant in pharmaceuticals (Ivashkiv & Dunham, 1973).

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[1] Calculated from: $mg/m^3 = (\text{relative molecular mass}/24.45) \times ppm$, assuming a temperature of 25 °C and a pressure of 101 kPa

Glycidol has become an important intermediate for the production of functional epoxides. For example, reaction of phosgene with glycidol yields 2,3-epoxypropyl chloroformate. Reaction of glycidol with isocyanates affords the commercially important glycidyl urethanes (Sienel *et al*., 1987). It is used as an intermediate in the production of pharmaceuticals, as an additive for synthetic hydraulic fluids and as a reactive diluent in some epoxy resin systems (Hooper *et al*., 1992; American Conference of Governmental Industrial Hygienists, 1999). It is a stabilizer for natural oils and vinyl polymers, a dye-levelling agent and a demulsifier (American Conference of Governmental Industrial Hygienists, 1986).

1.4 Occurrence

1.4.1 *Natural occurrence*

Glycidol is not known to occur as a natural product.

1.4.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1999), as many as 4900 workers in the United States were potentially exposed to glycidol (see General Remarks). National estimates of workers potentially exposed in other countries were not available.

1.4.3 *Environmental occurrence*

Production of glycidol and its broad applications as an intermediate, as a reactive diluent in epoxy resins and as a stabilizer and a sterilant may result in its release into the environment through various waste streams (Ivashkiv & Dunham, 1973; Kaplan *et al*., 1982; Nomeir *et al*., 1995; Department of Health and Human Services, 1999).

1.5 Regulations and guidelines

Occupational exposure limits and guidelines for glycidol are presented in Table 1.

2. Studies of Cancer in Humans

No data were available to the Working Group.

Table 1. Occupational exposure limits and guidelines for glycidol[a]

Country	Year	Concentration (mg/ m^3)	Interpretation[b]
Australia	1993	75	TWA
Belgium	1993	75	TWA
Denmark	1993	1	STEL
Finland	1998	150 (sk)	TWA
		225	STEL
France	1993	75	TWA
Germany	1999	150	TWA
Ireland	1997	75	TWA
Netherlands	1997	150	TWA
Philippines	1993	150	TWA
Russian Federation	1993	5	STEL
Switzerland	1993	75	TWA
		150	STEL
Turkey	1993	150	TWA
United States			
ACGIH	1999	6.1 (A3)[c]	TWA
NIOSH	1999	75	TWA
OSHA	1999	150	TWA

[a] From Finnish Ministry of Social Affairs and Health (1998); American Conference of Governmental Industrial Hygienists (ACGIH) (1999); Deutsche Forschungsgemeinschaft (1999); Occupational Safety and Health Administration (OSHA) (1999)
[b] TWA, time-weighted average; STEL, short-term exposure limit; A3, confirmed animal carcinogen with unknown relevance to humans; sk, skin notation
[c] These countries follow the recommendations of the ACGIH threshold limit values: Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, nine weeks of age, were administered 0, 25 or 50 mg/kg bw of glycidol (94% purity, with the primary impurity, as determined by gas chromatography, being diglycidyl ether at a concentration of 2.8%, and 3-methoxy-1,2-propanediol (1.2%), 2,6-dimethanol-1,4-dioxane (1.1%), 3-chloro-1,2-propanediol (0.4%) and methanol (0.1%) as lesser impurities) in distilled water by gavage on five days per week for 103 weeks. The survival of female mice at the high dose was significantly lower after week 101 than in the controls. As shown in Table 2, there was a significantly increased incidence of Harderian gland adenomas

Table 2. Incidence of primary tumours in B6C3F$_1$ mice exposed to glycidol

Tumour site	Animals with tumours					
	Males			Females		
	0 mg/kg bw	25 mg/kg bw	50 mg/kg bw	0 mg/kg bw	25 mg/kg bw	50 mg/kg bw
Harderian gland[a]	8/46	12/41	22/44***	4/46	11/43*	17/43***
Forestomach[b]	0/50	2/50	9/50***	3/50	5/50	4/50
Liver[c]	24/50	31/50	35/50**	9/50	7/50	14/50
Mammary gland[d]				1/50	5/50	15/50***
Lung[e]	13/50	11/50	21/50*	3/50	4/50	5/50
Skin[b]	0/50	0/50	4/50*	–	–	–
Subcutis[f]	11/50	3/50	4/50	0/50	3/50	9/50***
Uterus[g]	–	–	–	0/50	3/50	3/50

From Irwin *et al.* (1996)
bw, body weight
[a] Adenomas and adenocarcinomas
[b] Squamous-cell papillomas
[c] Hepatocellular adenomas and carcinomas
[d] Adenocarcinomas
[e] Alveolar/bronchiolar adenomas or carcinomas
[f] Sarcomas and fibrosarcomas
[g] Carcinomas and adenocarcinomas
* $p \leq 0.05$; Fisher's exact test or incidental tumour test
** $p \leq 0.01$; Fisher's exact test
*** $p \leq 0.001$; Fisher's exact test

and adenocarcinomas combined in the high-dose males and in the high- and mid-dose females, and of Harderian gland adenocarcinomas in the high-dose males. In male mice only, the incidences of adenomas and carcinomas of the liver, squamous-cell papillomas of the forestomach and skin and alveolar/bronchiolar adenomas of the lung were significantly increased at the high dose; in females only, the incidences of mammary gland adenocarcinomas and of subcutaneous sarcomas and fibrosarcomas combined were significantly increased at the high dose. There was also a slight increase in uterine glandular carcinomas in female mice (National Toxicology Program, 1990; Irwin *et al*., 1996).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, eight weeks of age, were administered 0, 37.5 or 75 mg/kg bw of glycidol (purity, 94%, with the main impurities being those listed in Section 3.1.1) in distilled water by gavage on five days per week for 103 weeks. Survival of rats was significantly lower in the treated groups in both males and females than in the control groups, with the mean survival being 92, 82 and 66 weeks for the control, mid- and high-dose males, respectively, and 97, 85 and 78 weeks for the female dose groups. As shown in Table 3, there was a statistically significant increase in the incidence of mesotheliomas of the tunica vaginalis/peritoneum in males at both 37.5 and 75 mg/kg bw. There was a statistically significant increase in the incidence of fibroadenoma and adenocarcinoma of the mammary gland in female rats, and of mammary fibroadenoma in male rats at both doses in each case. The incidences in the forestomach of squamous-cell papilloma and of squamous papilloma or carcinoma combined were significantly increased in female rats at both doses and in male rats at the high dose. Gliomas of the brain were significantly increased in both sexes at the high dose. Other tumour types with increased incidence included squamous-cell papillomas or carcinomas of the mouth or tongue, adenomas or carcinomas of the clitoral gland and leukaemia in female rats; and Zymbal gland carcinomas, thyroid follicular-cell adenomas or carcinomas, skin tumours and adenomatous polyps or adenocarcinomas of the intestine combined in male rats (National Toxicology Program, 1990; Irwin *et al*., 1996).

3.1.3 *Hamster*

Groups of 20 male and 20 female Syrian golden hamsters, 10 weeks of age, were administered 0.2 mL glycidol solution (96% purity with ‘varying amounts of polymer’) in a 1:1 mixture of ethyl acetate and corn oil, representing a dose of 12 mg glycidol (approximately 100 mg/kg bw) by gavage twice a week for 60 weeks. This was calculated to amount to a total dose of 1.45 g per animal. Groups of 12 male and 12 female hamsters given 0.2 mL ethyl acetate:corn oil for 90 weeks comprised the controls. Survival was similar among the groups, with the median week of death being

Table 3. Incidence of primary tumours in Fischer 344/N rats exposed to glycidol

Site/tumour	Animal with tumours[a]					
	Males			Females		
	0 mg/kg bw	37.5 mg/kg bw	75 mg/kg bw	0 mg/kg bw	37.5 mg/kg bw	75 mg/kg bw
Tunica vaginalis/peritoneum[b]	3/49	34/50***	39/47***	–	–	–
Brain[c]	0/46	5/50*	6/30**	0/49	4/46*	4/46**
Clitoral gland[d]	–	–	–	5/49	9/47	12/45*
Forestomach[e]	1/46	2/50	6/32*	0/47	4/38*	11/30***
Haematopoietic system[f]	25/50	33/50	21/50	13/49	14/44	20/41*
Intestine[g]	0/47	1/50	4/37*	–	–	–
Mammary gland[h]	3/45	8/39	7/17**	14/50	34/50***	37/50***
Mouth/tongue[i]	3/50	2/50	5/50	1/46	3/37	7/26**
Skin[j]	0/45	5/41*	4/18*	–	–	–
Thyroid gland[k]	1/46	4/42	6/19**	0/50	1/50	3/49
Zymbal's gland[l]	1/49	3/50	6/48*	–	–	–

From Irwin *et al.* (1996)

[a] Effective numbers (number of animals with tumours among the number of animals surviving at the appearance of the first tumour)

[b] Mesotheliomas

[c] Gliomas

[d] Adenomas and carcinomas

[e] Squamous-cell papillomas and carcinomas

[f] Leukaemia

[g] Adenomatous polyps and adenocarcinomas

[h] Fibroadenomas and adenocarcinomas

[i] Sebaceous gland adenomas and carcinomas or basal-cell tumours

[j] Follicular-cell adenomas and carcinomas

[k] Carcinomas

* $p \leq 0.05$; Fisher's exact test or incidental tumour test

** $p \leq 0.01$; Fisher's exact test

*** $p \leq 0.001$; Fisher's exact test

97, 92, 84 and 84 for control males, treated males, control females and treated females, respectively. There was no statistically significant increase in the incidence of tumours in any target organ. However, 2/19 males and 4/20 females had haemangiosarcomas of the spleen compared with 0/12 male and 0/12 female controls (Lijinsky & Kovatch, 1992).

3.2 Skin application

3.2.1 *Mouse*

A group of 20 female ICR/Ha Swiss mice, eight weeks of age, was administered glycidol (commercial grade purified by distillation under vacuum) by skin painting onto the dorsal skin three times per week for 520 days at a concentration of 5% in acetone. Control groups of 100 female mice of the same strain each included three 100% acetone-treatment and three no-treatment groups, with the vehicle administered in the same way. Survival was similar between groups. Under this regimen, glycidol did not induce skin damage or skin tumours (Van Duuren *et al*., 1967).

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*

Glycidol is rapidly hydrolysed to glycerol (97.2%) and α-chlorohydrin (3-chloro-1,2-propanediol, 2.8%) in 0.1 M hydrochloric acid, with a half-life of 10 min. At pH 7 or 8, glycidol readily reacts with glutathione to form *S*-(2,3-dihydroxypropyl)glutathione (Jones, 1975).

Approximately 87–92% of 37.5 or 75 mg/kg body weight (bw) orally administered glycidol is absorbed from the gastrointestinal tract of male Fischer 344 rats. Seven to eight per cent of the dose remained in tissues 72 h following administration. The highest concentrations of radioactivity were observed in blood cells, thyroid, liver, kidney and spleen (Nomeir *et al.*, 1995).

S-(2,3-Dihydroxypropyl)glutathione, *S*-(2,3-dihydroxypropyl)cysteine and β-chlorolactic acid are the major metabolites isolated from rat urine after intraperitoneal administration of glycidol. The generation of β-chlorolactic acid is presumably a result of initial formation of α-chlorohydrin, with subsequent oxidation by alcohol and aldehyde

dehydrogenases. Glycidol is hydrolysed to glycerol by rat liver microsomal preparations (Jones, 1975; Jones & O'Brien, 1980; Patel *et al.*, 1983).

A single dose by gavage of 500 μL/kg [560 mg/kg] bw glycidol to male Wistar rats led to significant decreases in hepatic glutathione content between 30 min and 12 h after treatment. Recovery was complete by 24 h. The decrease in glutathione content 2 h after dosing with 750 μL/kg [840 mg/kg] bw was no greater than that observed after dosing with 150 μL/kg [168 mg/kg] bw (Montaldo *et al.*, 1984).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

No histopathological or serum enzyme signs of liver damage were observed in male Wistar rats dosed by gavage with up to 750 μL/kg [840 mg/kg] bw glycidol (Montaldo *et al.*, 1984).

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 30–37 pregnant CD-1 mice were treated with glycidol by gavage at dose levels of 0, 100, 150 or 200 mg/kg bw per day on days 6–15 of gestation, and then killed on day 18 of gestation. Five of the 30 dams died in the highest-dose group. There was no reduction in the total number of implantations and no increase in the numbers of resorptions or fetal deaths per pregnancy, or morphological variations that could be directly attributed to the treatment. In the highest-dose group, one litter consisted of 15 stunted fetuses, among which six had cleft palates. However, all 15 stunted fetuses were attributable to a single dam (Marks *et al.*, 1982).

Groups of pregnant Sprague-Dawley rats [numbers not specified] were laparotomized on day 13 of gestation and the embryos of one uterine horn were given intra-amniotic injections of glycidol in 0.9% sodium chloride at dose levels of 10, 100 and 1000 μg per fetus. The contrauterine horn embryos received intra-amniotic injections of 0.9% sodium chloride. The dams were killed on day 20 of gestation. Throughout the treated groups, there was an approximately 50% resorption frequency. No malformed fetuses were observed in the saline-treated uterine horns or in the glycidol-treated horns

at the lower doses, but 44% of the surviving fetuses treated with 1000 μg glycidol were malformed. The commonest malformations were of the forelimbs (39%), hindlimbs (22%) and pinnae (11%) (Slott & Hales, 1985).

Adult male and female mice [strain not specified] were mated for 30 min and then groups of 23–31 females were treated with glycidol [route not stated] at dose levels of 0 or 250 mg/kg bw. The glycidol treatment was given at 1, 6, 9 or 25 h after mating and the mice were killed on gestational day 17. Resorptions were increased by glycidol treatment, from 3.2% in the controls to 11.6%, 15.0%, 10.6% and 7.9% in the 1-, 6-, 9- and 25-h treatment time groups, respectively. Late deaths and anomalies were also increased in the 1- and 6-h treatment time groups (Rutledge *et al*., 1992).

Groups of 34 female (SEC × C57BL6)F_1 mice were injected intraperitoneally once with 0 or 300 mg/kg bw glycidol and then mated the following morning with untreated (C3H/R1 × C57BL10)F_1 males. Newborn mice were looked for in the breeding cages beginning 18 days after pairing, and were counted and killed. This procedure was continued through 17 breeding intervals (approximately 347 days). There was no significant difference in the numbers of offspring per female between the treated (143.4) and control (147.8) groups (Bishop *et al*., 1997).

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 4 for references)

The genetic toxicity of glycidol has been reviewed (Ehrenberg & Hussain, 1981).

Glycidol gave a positive response in assays of prophage induction and SOS repair in *Escherichia coli*. Results were uniformly positive in several *Salmonella typhimurium* reverse mutation assays and in two fungal mutation assays. The sex-linked recessive lethal mutation assay and the heritable translocation test in *Drosophila melanogaster* also gave positive results.

In mammalian assays, glycidol has been tested in human lymphocytes and Chinese hamster cells *in vitro* for induction of chromosomal aberrations and sister chromatid exchanges. It was also tested *in vivo* in the mouse micronucleus assay. All test results were positive, as were those of gene mutation assays using Chinese hamster V79 cells and mouse lymphoma L5178Y cells. An in-vivo assay to detect chromosomal aberrations in mouse bone-marrow cells gave negative results.

The only mammalian assay to give no response without exogenous metabolism was an unscheduled DNA synthesis test using human cells. This test did, however, give a positive response in the presence of S9, which was also in contrast to the majority of the tests, in which the addition of an exogenous metabolizing system reduced the activity of the compound.

Table 4. Genetic and related effects of glycidol

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	–	NT	500 µg/plate	Mamber *et al*. (1984)
Escherichia coli PQ37, SOS chromotest	+	NT	244.5	von der Hude *et al*. (1990)
Escherichia coli pol A/W3110-p3478, differential toxicity (liquid suspension test)	+	NT	430 µg/well	McCarroll *et al*. (1981)
Escherichia coli WP2/WP100 *rec* assay, differential toxicity	+	NT	54 µg/well	McCarroll *et al*. (1981)
Escherichia coli WP2/WP100 *rec* assay, differential toxicity	+	NT	10 000 µg/plate	Mamber *et al*. (1984)
Salmonella typhimurium TA100, reverse mutation	+	NT	100 µg/plate	Wade *et al*. (1979)
Salmonella typhimurium TA100, reverse mutation	+	+	61.7 µg/plate	Thompson *et al*. (1981)
Salmonella typhimurium TA100, reverse mutation	+	+	33 µg/plate	Canter *et al*. (1986)
Salmonella typhimurium TA100, reverse mutation	+	NT	25 µg/plate	Claxton *et al*. (1991)
Salmonella typhimurium TA1535, reverse mutation	+	+	20.6 µg/plate	Thompson *et al*. (1981)
Salmonella typhimurium TA1535, reverse mutation	+	+	500 µg/plate	Mamber *et al*. (1984)
Salmonella typhimurium TA1535, reverse mutation	+	+	3 µg/plate	Canter *et al*. (1986)
Salmonella typhimurium TA1537, reverse mutation	(+)	+	1670 µg/plate	National Toxicology Program (1990)
Salmonella typhimurium TA98, reverse mutation (spot test)	–	NT	10 000 µg/plate	Wade *et al*. (1979)
Salmonella typhimurium TA98, reverse mutation	+	+	3333 µg/plate	National Toxicology Program (1990)
Salmonella typhimurium TA97, reverse mutation	+	+	333 µg/plate	National Toxicology Program (1990)
Escherichia coli (Sd-4), reverse mutation	+	NT	740	Hussain (1984)
Klebsiella pneumoniae, forward mutation	+	NT	14.8	Voogd *et al*. (1981)
Schizosaccharomyces pombe, forward mutation	+	+	74	Migliore *et al*. (1982)
Neurospora crassa, reverse mutation	+	NT	37 000[c] (15 min)	Kolmark & Giles (1955)
Drosophila melanogaster, sex-linked recessive lethal mutations	+		1230 in feed	Foureman *et al*. (1994)

Table 4 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Drosophila melanogaster, heritable translocation test	+		1230 in feed	Foureman *et al*. (1994)
Gene mutation, Chinese hamster lung V79 cells, 6-thioguanine resistance *in vitro*	+	NT	0.15	Smith *et al*. (1990)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	+	8	Thompson *et al*. (1981)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	NT	1.43	National Toxicology Program (1990)
Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	1.11	National Toxicology Program (1990)
Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	+	NT	92.6	von der Hude *et al*. (1991)
Chromosomal aberrations, Chinese hamster cells *in vitro*	+	+	12.5	National Toxicology Program (1990)
Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	3.7	Norppa *et al*. (1981)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	29.6	Norppa *et al*. (1981)
Micronucleus formation, B6C3F$_1$ mice *in vivo*	+		150 ip × 2	National Toxicology Program (1990)
Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		226 po × 5	Thompson & Hiles (1991)
Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		145 ip × 5	Thompson & Hiles (1991)

[a] +, positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; *Drosophila* tests, ppm; po, oral; ip, intraperitoneal

[c] One dose tested; time-dependent response

Glycidol has been demonstrated to alkylate DNA in a number of in-vitro studies (Hemminki, 1979, Hemminki *et al*., 1980; Hemminki, 1983; Djuric & Sinsheimer, 1984a,b; Djuric *et al*., 1986; Segal *et al*., 1990).

4.5 Mechanistic considerations

Glycidol possesses a reactive epoxide moiety. This is likely to be responsible for the genotoxic activity of the compound without a requirement for metabolic activation.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Glycidol is an epoxide used as a chemical intermediate in the production of functional epoxides, glycidyl urethanes, pharmaceuticals and other products. It is also used as a reactive diluent in epoxy resin systems and as a sterilant. Occupational exposure may occur during its production and use. No data were available on environmental exposure to glycidol.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Glycidol has been tested by oral administration in one study in mice, in one study in rats and in one study in hamsters. It was also tested by skin application in one study in mice. After oral administration to mice, it produced increases in tumours of the Harderian gland in both males and females, of the forestomach, lung, liver and skin in males, and of the mammary gland and subcutaneous tissue in females. In rats, it produced increases in the incidence of gliomas of the brain and forestomach tumours in both males and females. Mesotheliomas of the tunica vaginalis/peritoneum, as well as tumours of the intestine, skin, thyroid gland and Zymbal gland were increased in males. Tumours of the clitoral gland, mammary gland and oral mucosa as well as leukaemia were increased in females.

In hamsters, there was a marginal increase in the incidence of splenic haemangiosarcomas after oral administration.

No skin tumours were observed in mice after skin application.

5.4 Other relevant data

Glycidol is an alkylating agent which reacts readily with glutathione. It causes a decrease in glutathione content in rat liver, probably reflecting its binding to glutathione. In rats, it is metabolized to oxidative and glutathione-derived products. No toxicokinetic data on humans were available.

No data on developmental and reproductive effects in humans were available to the Working Group.

No effects on fertility or development were observed in mice given intraperitoneal injections of glycidol 24 h before mating or orally during organogenesis. In contrast, when a single dose of glycidol was administered to female mice within 25 h after mating, the numbers of fetal deaths and anomalies were increased. Intra-amniotic injection of glycidol on day 13 of gestation in rats increased the frequency of resorptions and, at high doses, limb malformations.

Glycidol has been shown to be genotoxic using assays covering a wide range of end-points. *In vitro*, it did not require metabolic activation to elicit positive responses.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of glycidol were available.

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that glycidol is a direct-acting alkylating agent that is mutagenic in a wide range of in-vivo and in-vitro test systems.

6. References

American Conference of Governmental Industrial Hygienists (1986) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th Ed., Cincinnati, OH, ACGIH®, p. 287

American Conference of Governmental Industrial Hygienists (1999) *TLVs and other Occupational Exposure Values—1999 CD-ROM*, Cincinnati, OH, ACGIH®

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