CHRONIC TOXICITY SUMMARY

GLUTARALDEHYDE

(1,5-pentanedial; 1,5-pentanedione; glutaric dialdehyde; Aldesen; Cidex; Sonacide)

CAS Registry Number: 111-30-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.08 µg/m^3** (0.02 ppb)
Critical effect(s)	Squamous metaplasia of the respiratory epithelium in the nose of male and female mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1996; CRC, 1994; Chemfinder, 2000)

Description	Colorless liquid/oil
Molecular formula	$C_5H_8O_2$
Molecular weight	100.12 g/mol
Boiling point	188°C (decomposes) (CRC, 1994)
Melting point	–6°C (Chemfinder, 2000)
Solubility	Soluble in water, alcohol, benzene
Conversion factor	4.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Glutaraldehyde is a chemical frequently used as a disinfectant and sterilizing agent against bacteria and viruses (2% solution), an embalming fluid and tissue fixative, a component of leather tanning solutions, and an intermediate in the production of certain sealants, resins, dyes, and electrical products (HSDB, 1996). For commercial purposes, solutions of 99%, 50%, and 20% are available. Glutaraldehyde is also an atmospheric reaction product of cyclohexene. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 29,603 pounds of glutaraldehyde (CARB, 2000).

IV. Effects of Human Exposure

Evidence of the toxicity of glutaraldehyde to humans is limited to reports of occupational exposure from its use as a disinfectant and sterilizing agent. Frequently observed effects from exposure include skin sensitivity resulting in dermatitis, and irritation of the eyes and nose with accompanying rhinitis (Jordan *et al.*, 1972; Corrado *et al.*, 1986; Hansen, 1983; Wiggins *et al.*, 1989). Occupational asthma has also been reported among workers repeatedly exposed

to glutaraldehyde, particularly respiratory technologists who use glutaraldehyde as a sterilizing agent for endoscopes (Chan-Yeung *et al.*, 1993; Stenton *et al.*, 1994; Gannon *et al.*, 1995). Quantitation of the exposure levels that led to glutaraldehyde sensitization was not available from the studies.

V. Effects of Animal Exposure

The histopathology of the respiratory tract in rats and mice exposed to glutaraldehyde by inhalation was examined (Gross *et al.*, 1994). F344 rats and B6C3F1 mice (20 animals of each sex and of each species at each exposure level for a total of 480 rodents) were continuously exposed to glutaraldehyde in recirculating exposure chambers at concentrations of 0, 62.5, 125, 250, 500, or 1000 ppb glutaraldehyde for one day, 4 days, 6 weeks, or 13 weeks. At termination, respiratory tract tissue as well as duodenum and any gross lesions were collected and formalin fixed. Animals were treated with tritiated thymidine two hours before termination to evaluate cell replication in certain respiratory tract tissues. Respiratory tract tissue sections were made as follows: transverse sections of the nose and trachea, frontal section of the carina, and longitudinal section of the lung. Ten male and 10 female mice exposed to 1000 ppb and one female mouse exposed to 500 ppb group died during the course of the study. Two male and 3 female rats exposed to 1000 ppb died during the course of the study. Histopathological examination of animals surviving to the end of the study entailed scoring the severity of the finding from “no response” to “very severe” response on a 0 to 5 scale. Unit length labeling index, the indicator of cell proliferation, was evaluated by autoradiography at two sites: the nasal vestibule and the dorsal atrioturbinate.

Lesions in animals treated with glutaraldehyde appeared primarily in the anterior third of the nose. Lesions were apparently more increased in mice compared to rats due to some level of “background” non-suppurative lesions in the rats. Mice were considered devoid of background lesions. In the 13-week study, female mice were the most sensitive, with lesions averaging a score of 2 (mild and clear, but of limited extent and/or severity). The lesions were characterized as neutrophilic infiltration primarily in the squamous epithelium of the vestibule, with thickening of the epithelium leading to loss of the characteristic surface grooves. Both cell size and number were reported to be increased. Lesions were generally found to increase in nature and severity with increased time and level of exposure. Obstruction of the nasal vestibule was thought to account for the mortality of animals in the higher dose groups. In female mice at 13 weeks, all glutaraldehyde dose groups showed the accumulation of eosinophilic proteinaceous deposits in the respiratory epithelium of the maxilloturbinate margin. Examination of unit length labeling indices as a measure of growth showed significant increases in all treated groups of female mice. No evidence of exposure related lesions was found in the respiratory tract in the trachea, carina, bronchi, or lungs.

Mean Subjective Pathology Scores for Nasal Lesions in Female Mice at 13 Weeks

	Glutaraldehyde	*Intraepithelial neutrophils*	*Subepithelial neutrophils*	*Squamous metaplasia*
	0 ppb	0	0.4	0
	62.5 ppb	2.0	2.0	0
	125 ppb	2.4	2.8	0
	250 ppb	3.2	3.2	0
	500 ppb	2.8	2.8	0.5
	1000 ppb*	--	--	--

*Animals exposed to 1000 ppb died early in the experiment.

Greenspan *et al.* (1985) exposed male and female F-344 rats to 0, 0.3, 1.1 and 3.1 ppm glutaraldehyde and 0, 0.2, 0.63, and 2.1 ppm glutaraldehyde, respectively, in a 9-day study, and both sexes to 0, 21, 49, and 194 ppb glutaraldehyde in a 14 week study. Animal numbers were not specified. Exposures were conducted for 6 hours per day, 5 days per week. In the 9-day study, observations in the high and intermediate dose level groups included reduced body weight gain, inflammation of the nasal and olfactory mucosa, and sensory irritation. In the two highest doses of the 14-week study, statistically significant differences in body weight gain were observed as well as perinasal wetness. No histopathological indication of inflammation in olfactory or nasal mucosa was observed.

Mice were exposed to 0, 0.3, 1.0, and 2.6 ppm glutaraldehyde vapors for 6 hours/day for 4, 9, or 14 days (Zissu *et al.*, 1994). These mice were killed immediately after the exposure period. Other groups exposed to 1.0 ppm for 14 days were killed after recovery periods of 1, 2, and 4 weeks. After 4 days of exposure to the lowest dose, mice showed lesions in the respiratory epithelium of the septum, and the naso- and maxilloturbinates. After exposure to 1.0 ppm glutaraldehyde, lesions were still judged as severe after 2 weeks of recovery.

A study comparing the effects of intra-nasally instilled glutaraldehyde and formaldehyde on rat nasal epithelium found inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia in treated animals (St. Clair *et al.*, 1990). Acute inhalation exposure to formaldehyde produced identical lesions. Ten-fold higher concentrations of instilled formaldehyde were required to produce the same effect as instilled glutaraldehyde.

In a chronic study, NTP (1998, 1999) exposed groups of 50 male and 50 female F344/N rats to 0, 250, 500, or 750 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of 500 and 750 ppb female rats was less than that of the chamber controls. Mean body weights of all exposed groups of male rats and 500 and 750 ppb female rats were generally less than those of the chamber controls. Increased incidences of nonneoplastic nasal lesions occurred primarily within the anterior section of the nose in 500 and 750 ppb rats and to a lesser extent in 250 ppb rats. The more significant lesions included hyperplasia and inflammation of the squamous and respiratory epithelia and squamous metaplasia of the respiratory epithelium. Thus 250 ppb (1000 $\mu g/m^3$) is a chronic LOAEL for rats.

In the same study NTP (1998, 1999) exposed groups of 50 male and 50 female B6C3F1 mice to 0, 62.5, 125, or 250 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of female mice exposed to 250 ppb were generally less than those of the controls. The incidence of inflammation of the nose was marginally increased in 250 ppb females. Incidences of squamous metaplasia of the respiratory epithelium were increased in 250 ppb males and females and 125 ppb females. Incidences of hyaline degeneration of the respiratory epithelium were increased in all exposed groups of females. Thus 62.5 ppb was a chronic LOAEL for female mice.

Incidence of Nasal Lesions in Female Mice exposed for 104 weeks

	Glutaraldehyde	*Inflammation*	*Respiratory epithelium hyaline degeneration*	*Respiratory epithelium squamous metaplasia*
	0 ppb	6/50	16/50	7/50
	62.5 ppb	7/49	35/49	11/49
	125 ppb	13/50	32/50	16/50
	250 ppb	14/50	30/50	21/50

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP 1998, 1999
Study population	Male and female F344 rats and B6C3F1 mice (50/sex/group)
Exposure method	Continuous inhalation exposure (0, 62.5, 125, and 250 ppb in mice; 0, 250, 500, or 750 ppb in rats)
Critical effects	Respiratory epithelium squamous metaplasia
LOAEL	62.5 ppb (female mice)
NOAEL	Not observed
BMC_{05}	20.5 ppb
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	104 weeks
Equivalent continuous exposure	3.7 ppb (20.5 x 6/24 x 5/7)
Human equivalent concentration	0.62 ppb (gas with extrathoracic respiratory effects, RGDR = 0.17, BW = 28 g, MV = 0.032 L/min, SA = 3 cm^2)
LOAEL uncertainty factor	not needed in BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 ppb (0.08 µg/m^3)

Several studies indicate that the upper respiratory tract is a target for the toxicity of glutaraldehyde from inhalation exposure. Reports of toxicity to humans show that exposure can lead to occupational asthma as well as cause irritation of the eyes and nose with accompanying rhinitis. Likewise, animals exposed to glutaraldehyde by the inhalation route show evidence of respiratory irritation with the induction of lesions of the anterior nasal cavities upon long-term exposure (Gross *et al.*, 1994; Greenspan *et al.*, 1985; NTP, 1998, 1999). The NTP (1998, 1999) study yielded a chronic LOAEL for female mice of 62.5 ppb. Gross *et al.* (1994) showed neutrophilic infiltration in the olfactory epithelium in the lowest dose exposure group. (Female mice exposed to 62.5 ppb also showed subepithelial neutrophilic infiltration.) This level was taken to be the subchronic LOAEL. This effect on the nasal epithelium was demonstrated to be both concentration- and exposure duration-dependent.

A benchmark concentration was determined using EPA's version 1.20 BMC software and the dose-response data on respiratory epithelium squamous metaplasia in female mice. The quantal-linear model gave an MLE_{05} of 31.24 ppb, a BMC_{05} of 20.51 ppb, and a p value of 0.9471. With the benchmark approach no LOAEL UF is needed. The study was a lifetime study so the subchronic UF is 1. An interspecies UF of 3 rather than 10 was used since an RGDR adjustment had been made. The default intraspecies UF of 10 was used so that the total UF was 30. The resulting chronic REL for glutaraldehyde is 0.02 ppb (0.08 $\mu g/m^3$).

For comparison with the proposed REL, the study of Gross *et al*. (1994) used 62.5 ppb continuous exposure. Multiplying by the RGDR of 0.17 and dividing by a cumulative uncertainty factor of 300 (3 for a LOAEL, 3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL of 0.035 ppb (0.1 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation REL for glutaraldehyde is the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of human data, the lack of reproductive and developmental toxicity studies, the lack of dermal sensitization studies, and the lack of observation of a NOAEL.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Chan-Yeung M, McMurren T, Catonio-Begley F, and Lam S. 1993. Occupational asthma in a technologist exposed to glutaraldehyde. J. Allergy Clin. Immunol. 91:974-978.

Chemfinder, 2000. Available online at http://www.chemfinder.com

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Corrado OJ, Osman J, and Davies RJ. 1986. Asthma and rhinitis after exposure to glutaraldehyde. Hum. Toxicol. 5:325-328.

Gannon PF, Bright P, Campbell M, O'Hickey SP, and Burge PS. 1995. Occupational asthma to glutaraldehyde and formaldehyde in endoscopy and x-ray departments. Thorax 50:156-159.

Greenspan BJ, Ballantyne B, Fowler EH, and Snellings WM. 1985. Subchronic inhalation toxicity of glutaraldehyde. Toxicologist 5:29 (abstract).

Gross EA, Mellick PW, Kari FW, Miller FJ, and Morgan KT. 1994. Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam. Appl. Toxicol. 23:348-362.

Hansen KS. 1983. Glutaraldehyde occupational dermatitis. Contact Dermatitis 9:81-82.

HSDB. 1996. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Jordan WP, Dahl MV, and Albert HL. 1972. Contact dermatitis from glutaraldehyde. Arch. Dermatol. 105:94-95.

National Toxicology Program (NTP). 1998. Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS NO. 111-30-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). TR-490. Board Draft.

National Toxicology Program (NTP). 1999. Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS NO. 111-30-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). TR-490. September 1999. NIH Publication No. 99-3980. Available online at http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr490.html

St. Clair MBG, Gross EA, and Morgan KT. 1990. Pathology and cell proliferation induced by intra-nasal instillation of aldehydes in the rat: comparison of glutaraldehyde and formaldehyde. Toxicol. Pathol. 18:353-361.

Stenton SC, Beach JR, Dennis JH, Keaney NP, and Hendrick DJ. 1994. Glutaraldehyde, asthma and work -- a cautionary tale. Occup. Med. 44:95-98.

Wiggins P, McCurdy SA, and Zeidenberg W. 1989. Epistaxis due to glutaraldehyde exposure. J. Occup. Med. 31:854-856.

Zissu D, Gagnaire F, and Bonnet P. 1994. Nasal and pulmonary toxicity of glutaraldehyde in mice. Toxicol. Lett. 71:53-62.