

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO GLUTARALDEHYDE IN THE UNITED STATES

Glutaraldehyde is a commercial chemical used primarily as a disinfectant and biocide. It has numerous uses in industrial, agricultural, and medical settings, including: leather tanning; chemical intermediate; industrial antimicrobial agent and pesticide (algaecide, bactericide, and fungicide); biological tissue fixative; protein and polyhydroxy material cross-linking; x-ray processing; embalming fluid; printing industry preservative; poultry house fogging and other agricultural sanitization; as a materials preservative; intermediate for adhesives, sealants, and pharmaceuticals; and in the paper and textile industries. One of the main uses of glutaraldehyde is in cold sterilization of medical and dental equipment bronchoscopes.

Glutaraldehyde may be released to the environment through its production and use. It may be released to the atmosphere from its uses in x-ray development, as a disinfectant, and as a slimicide in paints and laundry detergents. It can also be released to air from oil and gas recovery and pipeline operations, industrial water treatment processes, poultry house fogging, and vehicle emissions. Glutaraldehyde releases to water generally occur as a result of waste water disposal from hospitals, textile and paper industries, industrial water treatment processes, cooling water systems, leather tanning, and oil and gas operations. When glutaraldehyde solutions are disposed of as sewage, residues can be released to water following sewage treatment processes. Disposal of cold disinfectant solutions from hospitals is the major source of glutaraldehyde to surface waters.

Glutaraldehyde is not considered to be highly persistent in the environment. It generally stays in the aquatic phase, where it rapidly degrades under both aerobic and anaerobic conditions. It is also expected to be highly mobile in soil, where it biodegrades under aerobic conditions. Glutaraldehyde does not bioaccumulate in aquatic organisms.

Glutaraldehyde has been identified in indoor and outdoor air as well as waste water samples. The majority of the atmospheric monitoring has been done in hospitals and dental clinics where glutaraldehyde is used for sterilization, where the highest concentrations generally occur near the source of sterilization equipment. Glutaraldehyde releases to indoor air are often mitigated by proper ventilation and handling techniques. Glutaraldehyde has been measured in waste water, primarily for waste streams originating from hospitals where glutaraldehyde solutions are regularly disposed of as sewage.

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Exposure to glutaraldehyde is primarily through inhalation, although dermal contact and ingestion may also occur. The general public is generally not exposed to glutaraldehyde, as it is primarily used in industrial or medical applications. People may be exposed in medical facilities or other areas where glutaraldehyde solutions are used for cleaning, and from paint and laundry detergents that contain glutaraldehyde. Although glutaraldehyde is used as a disinfectant for poultry/livestock equipment and processing premises, because it degrades so rapidly, the potential for glutaraldehyde residues to contaminate food sources is very slight. Medical and dental personnel are primarily at risk for occupational exposure to glutaraldehyde due to its use in disinfecting products and x-ray film processing. Occupational exposure may also occur as a result of paper manufacturing, oil and gas recovery and pipeline activities, animal house fogging and cleaning, metalworking, and other industrial processes where glutaraldehyde is used or produced.

### 2.2 SUMMARY OF HEALTH EFFECTS

Relevant information regarding glutaraldehyde toxicity in humans and laboratory animals subjected to systematic review (see Appendix B for detailed description of the systematic review process) and summarized in Section 3.2 of this Toxicological Profile for Glutaraldehyde. A brief overview of the information in Section 3.2 follows.

Glutaraldehyde is a contact irritant, dermal sensitizer, and potential respiratory sensitizer. Occupational exposure to glutaraldehyde has been commonly associated with symptoms of respiratory tract irritation, particularly in medical facilities where glutaraldehyde is used as a disinfectant. In occupational settings where personal or workplace air sampling was performed, self-reported respiratory tract symptoms following short-term exposures occurred at concentrations as low as 0.05 ppm. Single and repeated exposure of laboratory animals to glutaraldehyde vapor results in clinical signs (e.g., nasal discharge, labored breathing, mouth breathing, audible respiration, rales, perinasal encrustation) and histopathologic nasal lesions (e.g., rhinitis, epithelial changes, mild atrophy of olfactory mucosa) at airborne concentrations as low as 0.0625–2.6 ppm. Repeated-exposure scenarios result in exposure concentration-related increased incidence and severity of clinical signs and histopathologic nasal lesions. Glutaraldehyde-induced histopathologic lesions in animals are generally confined to the anterior nasal cavity.

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Glutaraldehyde irritates eyes and skin upon direct contact. Occupational exposure to glutaraldehyde has been commonly associated with ocular irritation and severe dermal irritation. Severe ocular effects were reported in patients undergoing eye surgical procedures; it was suspected that the effects were elicited by glutaraldehyde residue on surgical equipment following disinfection with glutaraldehyde-containing products. Glutaraldehyde induces contact ocular and dermal irritation in laboratory animals as well.

Pathologic evidence of glutaraldehyde-induced gastrointestinal irritation was observed following administration of aqueous glutaraldehyde by single gavage to rats and mice at sublethal and lethal doses. Gross and/or histopathologic respiratory lesions have been observed in some animals that were administered glutaraldehyde by the oral exposure route and likely resulted from the release of glutaraldehyde vapor from the digestive tract.

Depressed body weight gain or actual body weight loss was observed in some studies of animals repeatedly exposed to glutaraldehyde by inhalation, oral, or dermal routes. Increased incidences of self-reported headaches were noted among workers exposed to glutaraldehyde during disinfection processes. However, glutaraldehyde-induced neurotoxicity has not been demonstrated in animals.

Numerous reports suggest that glutaraldehyde causes dermal sensitization in occupational settings where glutaraldehyde is used as a germicide. The dermal sensitization potential of glutaraldehyde was not demonstrated in limited controlled human studies. Evidence of glutaraldehyde-induced dermal sensitization was noted in some animal studies.

There is some evidence for glutaraldehyde-induced respiratory hypersensitivity in occupationally-exposed individuals. Results from single-blind placebo-controlled studies of health workers with occupational exposure to glutaraldehyde and diagnosed with glutaraldehyde-induced occupational asthma and rhinitis suggest an immunologic mechanism. Other epidemiological studies revealed no evidence of glutaraldehyde-induced respiratory sensitization. There was no evidence of glutaraldehyde-induced respiratory sensitization in available animal studies.

Glutaraldehyde has been widely implicated as the cause of colitis and diarrhea following endoscopy or sigmoidoscopy procedures, the likely result of contact irritation.

The potential carcinogenicity of inhaled glutaraldehyde was assessed in a 2-year inhalation study of F344/N rats and B6C3F1 mice. Based on the lack of exposure-related increased incidences of neoplastic

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lesions in any organ or tissue from 2-year repeated exposures at up to 750 ppb (rats) and 250 ppb (mice), NTP concluded that there was “no evidence of carcinogenic activity” of glutaraldehyde. In another chronic study, increased incidences of large granular lymphocytic leukemia (LGLL) were noted in spleen and liver of female F344 rats administered glutaraldehyde in their drinking water at 50, 250, and 1,000 ppm. However, due to high background and variable incidences of LGLL in the Fischer 344 rat, statistical significance only in the female rats, and lack of a clear dose response, the study authors indicated that the biological significance of the LGLL findings was unclear and suggested that the statistical significance might possibly have been a result of an abnormally low incidence of LGLL in the control females. Furthermore, a Cancer Assessment Review Committee for the U.S. EPA did not consider the statistically increased incidences of LGLL to be treatment related because: (1) LGLL is a common and highly variable spontaneous neoplasm in F344 rats; (2) incidences were within the range of available historical control data; and (3) no significantly increased incidences of LGLL or any other tumors were seen in the male rats of this drinking water study, in male or female F344 rats or B6C3F1 mice exposed to glutaraldehyde vapor by inhalation for 2 years, or in Wistar rats exposed via the drinking water for 2 years. Glutaraldehyde is not on the list of agents evaluated for carcinogenicity by the International Agency for Research on Cancer. The American Conference of Governmental Industrial Hygienists (ACGIH) lists glutaraldehyde as A4 (not classifiable as a human carcinogen).

### 2.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 2-1, inhalation MRLs have been derived for acute- and intermediate-duration exposure to glutaraldehyde and an oral MRL has been derived for chronic-duration exposure to glutaraldehyde. The acute- and intermediate-duration inhalation MRLs are based on glutaraldehyde-induced nasal lesions in laboratory animals, the most sensitive end point identified from results of studies that employed acute- or intermediate-duration inhalation exposure scenarios. A chronic-duration inhalation MRL was not derived for glutaraldehyde because potential MRLs based on the most sensitive nasal lesions observed following chronic-duration inhalation exposure ( $\geq 1$  year) were 2–3-fold higher than the intermediate-duration inhalation MRL. Based on a conservative approach, this suggests that the intermediate-duration inhalation MRL would also be protective of chronic-duration inhalation exposure to glutaraldehyde. Insufficient data precluded the derivation of acute- or intermediate-duration oral MRLs for glutaraldehyde. Gastric irritation in chronically exposed rats served as the basis for deriving a chronic-duration oral MRL for glutaraldehyde. Refer to Section 3.6.2 and Appendix A for detailed information regarding MRL derivation for glutaraldehyde.

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**Table 2-1. Minimal Risk Levels (MRLs) for Glutaraldehyde<sup>a</sup>**

Exposure duration	Critical effect	Point of departure	Uncertainty factor	MRL
Inhalation exposure				
Acute	Nasal lesions observed in rats exposed to $\geq 0.250$ ppm (Gross et al. 1994; NTP 1993)	NOAEL <sub>HEC</sub> : 0.003 ppm	3 <sup>b</sup>	0.001 ppm
Intermediate	Nasal lesions observed in mice exposed to $\geq 0.0625$ ppm (Gross et al. 1994; NTP 1993)	BMCL <sub>10HEC</sub> : 0.00008 ppm	3 <sup>b</sup>	0.00003 ppm
Chronic	The intermediate-duration inhalation MRL is considered protective of longer-term exposure to glutaraldehyde because available animal data provide a less conservative MRL for chronic-duration inhalation exposure (0.00007 ppm)			
Oral exposure				
Acute	Insufficient data for derivation of an MRL			
Intermediate	Insufficient data for derivation of an MRL			
Chronic	Gastric irritation in rats exposed to $\geq 17$ mg/kg/day in drinking water (van Miller et al. 2002)	NOAEL: 4 mg/kg/day	30 <sup>c</sup>	0.1 mg/kg/day

<sup>a</sup>The respective exposure durations for acute, intermediate, and chronic MRLs are  $\leq 14$  days, 15–364 days, and  $\geq 1$  year.

<sup>b</sup>1 for extrapolation from animals to humans using dosimetric conversion and 3 for human variability.

<sup>c</sup>10 for extrapolation from animals to humans and 3 for human variability.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level