DRAFT
TOXICOLOGICAL PROFILE FOR
GLUTARALDEHYDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

December 2015

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Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.8	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.9	**Biomarkers of Exposure and Effect**
Section 3.12	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Clinical Resources

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for glutaraldehyde. The panel consisted of the following members:

1. Dr. H.M. Bolt, Leibniz Research Centre for Working Environment and Human Factors, Ardeystraβe 67, D-44139 Dortmund;

2. Dr. Barbara Shane, 205 Landreth Court, Durham, North Carolina; and

3. Dr. Errol Zeiger, Errol Zeiger Consulting, 800 Indian Springs Road, Chapel Hill, North Carolina.

These experts collectively have knowledge of glutaraldehyde's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT FOR GLUTARALDEHYDE

This Public Health Statement summarizes the Division of Toxicology and Human Health Science's findings on glutaraldehyde, tells you about it, the effects of exposure, and describes what you can do to limit that exposure.

If you are exposed to glutaraldehyde, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT IS GLUTARALDEHYDE?

Glutaraldehyde is a colorless, oily liquid with a sharp, pungent odor. Other names for glutaraldehyde include pentanedial, glutaral, and 1,5-pentanedial, as well as a variety of other chemical and trade names. Glutaraldehyde is not stable in its pure form, so it is usually found in a solution mixed with water.

Glutaraldehyde is used for industrial, laboratory, agricultural, and medical purposes, primarily for disinfecting and sterilization of surfaces and equipment. It may be found in medical facilities where it is used to disinfect equipment that cannot be subject to heat sterilization. It is also used in industrial cleaning supplies. The majority of the uses of glutaraldehyde are industrial as opposed to consumer applications. For example, it is used in oil and gas recovery, waste water treatment, as a pesticide and in fogging and cleaning of poultry houses, as a chemical intermediate in the production of various materials, in the paper industry, in x-ray processing, in embalming fluid, and for leather tanning. It may be used in select goods, such as paint and laundry detergent. Detailed information about the uses of glutaraldehyde can be found in Chapter 5.

WHERE IS GLUTARALDEHYDE FOUND?

Glutaraldehyde can get into air from its use as a disinfectant, such as in hospitals and dental clinics, and from other commodities that may use glutaraldehyde (e.g., paints). Industries using glutaraldehyde can also cause its release to air (e.g., oil and gas industry, animal facilities, and water treatment facilities). Glutaraldehyde in air will be degraded by light within a relatively short time period; that is, half will be gone from air in 16 hours.

Use of glutaraldehyde as a disinfectant can cause it to enter water, such as from hospital wastewater. Glutaraldehyde may enter groundwater during its use as a biocide for processes such as industrial water treatment or oil and gas recovery and pipeline operations. In water, glutaraldehyde will degrade quickly. Depending on how much oxygen is available in the water, glutaraldehyde might turn into carbon dioxide or 1,5-pentanediol.

Glutaraldehyde could get into soil in similar ways as it could get in to water. Contaminated water can seep into nearby soils. Glutaraldehyde will most likely disappear quickly from soil due to degradation. It is expected to travel quickly through soil.

HOW MIGHT I BE EXPOSED TO GLUTARALDEHYDE?

You are most likely to be exposed if you use products such as disinfectants that contain glutaraldehyde or if you are around areas that are being disinfected with glutaraldehyde-containing products. Because glutaraldehyde is used in oil and gas recovery operations (including hydrofracturing processes), there is potential for exposure among workers and the general population in areas surrounding such operations.

HOW CAN GLUTARALDEHYDE ENTER AND LEAVE MY BODY?

Most of the glutaraldehyde that you breathe in will react with tissue in your nose (or mouth and throat if you breathe it in through your mouth) and cause irritation; some may enter your blood.

You are not likely to come into contact with glutaraldehyde in drinking water. If you do, some of it would react with tissue in your gastrointestinal tract and cause irritation. Some might enter your blood.

You are not likely to come into contact with glutaraldehyde in soil. If you were to get glutaraldehyde on your skin, a very small amount might enter your blood.

Glutaraldehyde in the blood can travel throughout the body; it appears to rapidly break down into other substances including carbon dioxide.

Animal studies indicate that much of the glutaraldehyde that enters your blood is converted into carbon dioxide and leaves your body when you breathe it out. Some of the glutaraldehyde and/or its breakdown

products leave your body in the urine. If you were to drink water or eat food containing glutaraldehyde, more of it and/or its breakdown products would leave your body in the feces than in urine or exhaled air.

HOW GLUTARALDEHYDE CAN AFFECT YOUR HEALTH?

You are not likely to be exposed to amounts of glutaraldehyde that would harm you. If you were, the health effects would depend on the amount of glutaraldehyde to which you were exposed.

Your skin and eyes could become irritated if glutaraldehyde were to contact your skin and eyes. Your nose could become irritated if you were to breathe in glutaraldehyde. Your mouth, esophagus, and stomach could become irritated if glutaraldehyde were to enter your mouth.

Because glutaraldehyde causes irritation of tissues that come into contact with it, long-term effects are similar to those experienced by short-term exposure. Your skin might also become more sensitive to glutaraldehyde if you come into repeated contact with it.

There is no evidence that glutaraldehyde causes cancer in people. One study reported increases in a type of blood cancer in rats, but an EPA cancer assessment review committee concluded that this type of cancer was common in older rats. Other animal studies found no evidence that glutaraldehyde causes cancer.

The American Conference of Governmental Industrial Hygienists determined that glutaraldehyde is not classifiable as to whether it causes cancer based on available results from animal studies. Glutaraldehyde is not on the National Toxicology Program (NTP) list of known or suspected cancer-causing substances.

HOW CAN GLUTARALDEHYDE AFFECT CHILDREN?

This section discusses potential health effects of glutaraldehyde exposure in humans from when they’re first conceived to 18 years of age.

Glutaraldehyde is expected to affect children in the same manner as adults. It is not known whether children are more susceptible than adults to the effects of glutaraldehyde.

The few available reports for humans and animals have not shown that glutaraldehyde can cause birth defects.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO GLUTARALDEHYDE?

If your doctor finds that you have been exposed to significant amounts of glutaraldehyde, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Families are not likely to be exposed to glutaraldehyde, as it is primarily used in industrial or medical applications. However, in the event that a worker's clothing were to become soaked with glutaraldehyde, a change of clothes at the workplace would reduce the risk of exposing others outside the workplace environment.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO GLUTARALDEHYDE?

Although methods are available to detect glutaraldehyde in biological materials, they are not useful for estimating the magnitude of an exposure because glutaraldehyde reacts rapidly with tissues that it contacts. Also, absorbed glutaraldehyde leaves the body quickly as glutaraldehyde and/or its breakdown products.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or

a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

EPA has no drinking water standard for glutaraldehyde. OSHA has not established an exposure limit for glutaraldehyde in air. NIOSH established a Recommended Exposure Limit (REL) of 0.2 ppm in air, as a ceiling concentration.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. ATSDR can also provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

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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 as a disinfectant, in x-ray development, and from paints and laundry detergents that used it as a slimicide. 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.

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.

2. RELEVANCE TO PUBLIC HEALTH

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

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.

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 (≥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.

Table 2-1. Minimal Risk Levels (MRLs) for Glutaraldehyde[a]

Exposure duration	Critical effect	Point of departure	Uncertainty factor	MRL
Inhalation exposure				
Acute	Nasal lesions observed in rats exposed to ≥0.250 ppm (Gross et al. 1994; NTP 1993)	$NOAEL_{HEC}$: 0.003 ppm	3[b]	0.001 ppm
Intermediate	Nasal lesions observed in mice exposed to ≥0.0625 ppm (Gross et al. 1994; NTP 1993)	$BMCL_{10HEC}$: 0.00008 ppm	3[b]	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 ≥17 mg/kg/day in drinking water (van Miller et al. 2002)	NOAEL: 4 mg/kg/day	30[c]	0.1 mg/kg/day

[a]The respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.
[b]1 for extrapolation from animals to humans using dosimetric conversion and 3 for human variability.
[c]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

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of glutaraldehyde. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

ATSDR employed a systematic review of health effects data in preparation of this Toxicological Profile for Glutaraldehyde. The systematic review provides transparency regarding the process of identification, synthesis, and interpretation of the scientific evidence regarding potential hazards associated with inhalation, oral, and dermal/ocular exposure to glutaraldehyde. Details regarding the framework and implementation of the systematic review for glutaraldehyde-induced health effects are presented in Appendix B. Relevant data extracted from individual studies selected for inclusion in the systematic review were summarized (see Table B-2 of Appendix B). A summary of the extracted data for each study is available in the Supplemental Document for Glutaraldehyde. The available human and animal studies identified five potential health outcomes for glutaraldehyde: respiratory, gastrointestinal, renal, dermal, and ocular effects. Overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Section 3.2 of the profile and in the Levels Significant Exposure tables in Section 3.2 of the profile (Tables 3-1, 3-7, and 3-8, respectively).

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Dose response data for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Limited human data were located. Teta et al. (1995) found no evidence of increased mortality from any or all causes within a group of 186 workers assigned to glutaraldehyde production or drumming from 1959 to 1992 at a West Virginia facility when compared to the general U.S. population. Follow-up of this cohort resulted in similar findings (Collins et al. 2006).

No exposure-related deaths occurred in studies of rats exposed for 4–8 hours to saturated atmospheres of glutaraldehyde vapor generated under static conditions at temperatures ranging from 18 to 25°C (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991v; Union Carbide Corp. 1992a, 1992b). Studies that included analytical measurements under static conditions (test material placed in test chamber and atmosphere allowed to equilibrate) found average glutaraldehyde concentrations to measure <10 ppm. No deaths occurred among rats exposed for 4 or 8 hours to glutaraldehyde vapor under dynamic conditions (capable of generating higher glutaraldehyde vapor concentrations than under static conditions) at temperatures in the range of 17–23°C (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991p, 1991x; Union Carbide Corp. 1992a, 1992c). Studies that included analytical measurements under these conditions found glutaraldehyde vapor concentrations as high as 22.2 ppm. At air temperatures of 60–65°C within the vapor-generating system, glutaraldehyde vapor concentrations ranging from of 9.1 ppm to as high as 94.9 ppm were attained and resulted in 4-hour LC_{50} values of 23.5 and 40.1 ppm for male and female rats, respectively in one study (Union Carbide Corp. 1992l) and 37.2 and 53.1 ppm, respectively, in another study (Ballantyne 1995). Repeated 6-hour exposures (5 days/week for 9 exposures) of male and female rats to glutaraldehyde vapor at 3.1 ppm resulted in ≥50% mortality in

each gender (Union Carbide Corp. 1992d). Death was reported as early as day 3 in male mice exposed daily to glutaraldehyde vapor for 5 hours/day at 2.6 ppm (Zissu et al. 1994). All rats and mice repeatedly exposed to glutaraldehyde vapor concentrations ≥5 ppm (rats) and ≥1.6 ppm (mice) for 6 hours/day died between days 4 and 9 of 16-day studies (NTP 1993). In a 13-week repeated exposure study of rats and mice, all mice exposed at 1 ppm glutaraldehyde died during the first 5 weeks and 2/10 female mice of the 0.5 ppm exposure level died at weeks 7 and 8; there were no deaths among the exposed rats at the highest concentration (1 ppm) tested (NTP 1993). Similar effects on survival were observed in a time-course study designed to assess the effects of exposures to glutaraldehyde vapor for 1 or 4 days, or 6 or 13 weeks (Gross et al. 1994). In 2-year studies of rats, repeated exposure to glutaraldehyde vapor at 0.5 and 0.75 ppm resulted in significantly decreased survival of female (but not male) rats (15/50 and 14/50 0.5 and 0.75 ppm females, respectively, versus 26/50 control females); there was no significant effect on survival of similarly-exposed mice at the highest concentration (0.25 ppm) tested (NTP 1999).

All reliable LOAEL and LC_{50} values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each species, duration, and end point for systemic effects are recorded in Table 3-1 and plotted in Figure 3-1.

No information was located regarding the following systemic effects in humans exposed to glutaraldehyde by the inhalation route: gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, and dermal effects. No information was located regarding musculoskeletal or dermal effects in animals exposed to glutaraldehyde by the inhalation route.

Respiratory Effects. Results from controlled human studies and assessment of self-reported symptoms among workers that included measurements of airborne glutaraldehyde concentrations are summarized in Table 3-2. The glutaraldehyde odor threshold in humans was determined to be in the range of 0.0003 ppm based on multiple 5-second exposures; a similar exposure scenario resulted in a threshold of 0.47 ppm for the perception of an effect on nasal tissue (Cain et al. 2007). Within a group of 50 female subjects exposed to air only or glutaraldehyde vapor at 0.035, 0.050, 0.075, or 0.100 ppm for 15-minute intervals, the cumulative proportion of subjects who achieved 50% correct detection of glutaraldehyde (self-reported perception of nasal sensation) ranged from <5% at the glutaraldehyde

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
ACUTE EXPOSURE									
Death									
1	Rat (NS) 5 M, 5 F	Once (4 hr) 0, 11.0, 28.0, 37.2, 59.7, 94.9 ppm (measured)	CS LE				37.2 M 53.1 F	LC_{50} values 11.0 ppm: no deaths 28.0 ppm: 1.5 M, 1/5 F died 37.2 ppm 2/5 M, 0/5 F died 59.7 ppm: 5/5 M, 4/5 F died 94.9 ppm 5/5 M, 4/5 F died	Ballantyne 1995 Vapors generated at elevated temperature (60°C)
2	Rat (F344) 6 M, 6 F	Once (4 hr) 0, 10.6, 23.0, 42.7 ppm (measured)	CS FI GN HP LE WI				23.5 M 40.1 F	LC_{50} values 10 ppm: no deaths 20 ppm: 2/6 M, 2/6 F died 50 ppm: 6/6 M, 3/6 F died	Union Carbide Corp. 1992l Analytical concentrations from GC technique; Tenax trapping method resulted in slightly different analytical concentrations
3	Rat (F344) 5 M, 5 F	6 hr/d, 5 d/wk; up to 12 exposures 0, 0.16, 0.5, 1.6, 5, 16 ppm (target)	BW CS GN LE OW				5	All male and female rats of the 5 and 16 ppm exposure levels died by study day 9; no deaths at lower exposure levels	NTP 1993 Measured concentrations 96–100% of target
4	Rat (F344) 12 M, 12 F	6 hr/d, 5 d/wk; up to 9 exposures 0.3, 1.1, 3.1 ppm (measured)	BC BW CS FI GN HE HP LE OP OW UR WI				3.1	7/12 M, 6/12 F died; most deaths occurred during week 2 of exposures	Union Carbide Corp. 1992d
5	Rat (F344) 10 M, 10 F	6 hr/d, 5 d/wk; up to 9 exposures 0, 0.2, 0.63, 2.09 ppm (measured)	BW CS FI GN LE OP OW				2.09	9/10 M, 7/10 F died; most deaths occurred during latter half of study; one male rat of the 0.63 ppm died on final exposure day	Union Carbide Corp. 1992e
6	Mouse (B6C3F1) 5 M, 5 F	6 hr/d, 5 d/wk; up to12 exposures 0, 0.16, 0.5, 1.6, 5, 16 ppm (target)	BW CS GN LE OW				1.6	All male and female mice of the 1.6, 5, and 16 ppm exposure levels died by study day 8; no deaths at lower exposure levels	NTP 1993 Measured concentrations 94–101% of target
7	Mouse (Swiss OF1) 10 M	6 hr/d, 5d/wk; up to 9 exposures 0, 0.3, 0.9, 2.6 ppm (measured)	BW CS GN HP				2.6	4/10 died; mortalities occurred between days 3 and 5	Zissu et al. 1994

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
Systemic									
8	Human 40 F	Multiple 5-sec exposures 0.229-0.772 ppm (measured)	CS	Resp		0.47		0.47 ppm considered threshold for detection of glutaraldehyde-induced nasal tissue sensation (25/40 subjects identified exposure to glutaraldehyde correctly 50% of the time)	Cain et al. 2007
9	Human 5 M, 4 F	Multiple 2-min exposures during 3 d Multiple concentrations	CS	Resp		0.237–0.245		The threshold for nasal sensory irritation to activated (alkaline) glutaraldehyde solution was 0.237–0.245 ppm	Union Carbide Corp 1976 Accommodation to nasal irritation after 1 min frequently reported
10	Human 5 M, 4 F	Multiple 2-min exposures during 1 d; multiple concentrations	CS	Resp		0.255		The threshold for nasal sensory irritation to unactivated (acidic) glutaraldehyde solution was 0.255 ppm	Union Carbide Corp. 1976 Accommodation to nasal irritation after 1 min frequently reported
11	Human 50F	Multiple 15-min exposes 0.035, 0.050, 0.075, 0.1 ppm (measured)	CS	Resp		0.1		>50% of the subjects achieved 50% correct detection of glutaraldehyde (self-reported perception of nasal sensation) at 0.1 ppm	Cain et al. 2007
12	Rat (F344) 6 M, 6 F	Once (4 hr) 0, 10.6, 23.0, 42.7 ppm (measured)	CS FI GN HP LE WI	Resp BW	10.6		10.6	Clinical signs of respiratory irritation at all exposure levels increased in severity with increasing exposure concentration; body weight loss ranged from 14 to 30% of initial body weight and persisted for 7 days postexposure	Union Carbide Corp. 1992l Analytical concentrations from GC technique; Tenax trapping method resulted in slightly different analytical concentrations
13	Rat (F344) 5 M, 5 F	Once (6 hr) 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.125[b]	0.25		Exposure concentration-related increasing incidence and severity of nasal lesions; clinical signs (bloating, gasping) were noted at the “higher concentrations”	Gross et al. 1994 Statistical analysis not performed (only 5 animals/sex/group); analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
14	Rat (F344) 5 M, 5 F	6 hr/d for 4 d 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.25 M 0.125 F	0.5 M 0.25 F		Exposure concentration-related increasing incidence and severity of nasal lesions; clinical signs (bloating, gasping) were noted at the “higher concentrations”	Gross et al. 1994 Statistical analysis not performed (only 5 animals/sex/group); analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
15	Rat (F344) 12 M, 12 F	6 hr/d, 5 d/wk; up to 9 exposures 0.3, 1.1, 3.1 ppm (measured)	BC BW CS FI GN HE HP LE OP OW UR WI	Resp	0.3	1.1		Clinical signs of respiratory tract irritation at 1.1 and 3.1 ppm; histopathologic nasal lesions at 1.1 and 3.1 ppm included rhinitis, squamous metaplasia, and atrophy of olfactory mucosa	Union Carbide Corp. 1992d
16	Rat (F344) 10 M, 10 F	6 hr/d, 5 d/wk; up to 9 exposures 0, 0.2, 0.63, 2.09 ppm (measured)	BW CS FI GN LE OP OW	Resp BW	0.2	0.2		Exposure concentration-related increasing severity of clinical signs of respiratory tract irritation; depressed body weight gain (33-41% less than that of controls)	Union Carbide Corp. 1992e
17	Mouse (Swiss/ Webster 4 M	Once (30 min) 1.6, 3.99, 4.65, 5.6, 7.47, 17.7, 36.7 ppm (measured)	BW CS LE	Resp BW	36.7	1.6		Decreased respiratory rates almost immediately at all exposure levels, persisting throughout exposure	Werley et al. 1995 RD_{50}=13.86 ppm (95% CI 9.86–23.58)
18	Mouse (OF1) 6 M	Once (60 min) 0.7, 1.3, 1.7, 3.2, 4.3, 4.5 ppm (measured)	CS	Resp		0.7		Decreased respiratory rates almost immediately at all exposure levels with some recovery during the 60-minute exposure period	Zissu et al. 1994 RD_{50}=2.6 ppm
19	Mouse (B6C3F1) 5 M, 5 F	Once (6 hr) 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.25 M 0.125 F	0.5 M 0.25 F		Exposure concentration-related increasing incidence and severity of nasal lesions; clinical signs (bloating, gasping) were noted at the “higher concentrations”	Gross et al. 1994 Statistical analysis not performed (only 5 animals/sex/group); analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
20	Mouse (B6C3F1) 5 M, 5 F	6 hr/d for 4 d 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.125	0.25		Exposure concentration-related increasing incidence and severity of nasal lesions; clinical signs (bloating, gasping) were noted at the “higher concentrations”	Gross et al. 1994 Statistical analysis not performed (only 5 animals/sex/group); analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
21	Mouse (Swiss OF1) 10 M	6 hr/d, 5 d/wk; 4 or 9 exposures 0, 0.3, 1.0 ppm (measured)	BW CS GN HP	Resp		0.3		Nasal lesions (squamous metaplasia, keratin exudate, necrosis) in respiratory epithelium	Zissu et al. 1994

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
Immunological and Lymphoreticular Effects									
22	Guinea pig (Dunkin-Hartley) 4 M (control); 8 M (treated)	Induction: 1 hr/d for 5 d at 13.9 ppm (mean measured) Challenge: 1 hr/d for 3 d at 4.4 ppm (mean measured)	CS		13.9			No evidence of glutaraldehyde-induced respiratory sensitization	Werley et al. 1995
23	Mouse (BALB/c) 8 M	1.5 hr/d for 3 d at 0, 6, 18 ppm (target)	BW CS HP		18			No evidence of glutaraldehyde-induced respiratory sensitization	van Triel et al. 2011
Neurological Effects									
24	Rat (F344) 6 M, 6 F	Once (4 hr) 0, 10.6, 23.0, 42.7 ppm (measured)	CS FI GN HP LE WI		10.6		23	Impaired righting reflex following exposure at 42.7 ppm; decreased motor activity at 23 and 42.7 ppm persisting during 14 days of postexposure observation	Union Carbide Corp. 1992l Analytical concentrations from GC technique; Tenax trapping method resulted in slightly different analytical concentrations
INTERMEDIATE EXPOSURE									
Death									
25	Rat (F344) 5 M, 5 F	6 hr/d, 5 d/wk for 6 or 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE				1.0 M, F	2/20 M, 3/10 F died; deaths of rats scheduled for sacrifice at 6 or 13 weeks occurred during study week 3	Gross et al. 1994 Analytical concentrations within 99–104% of target
26	Mouse (B6C3F1) 5 M, 5 F	6 hr/d, 5 d/wk for 6 or 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE				1.0 M 0.5 F	All 1.0 ppm male and female mice scheduled for sacrifice at 6 or 13 weeks died during study weeks 2–7; one 0.5 ppm female mouse died	Gross et al. 1994 Analytical concentrations within 99–104% of target
27	Mouse (B6C3F1) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW				1.0 M 0.5 F	All 1.0 ppm male and female mice died; most deaths occurred between weeks 1 and 3; deaths (2/10) in 0.5 ppm females occurred at weeks 7 and 8	NTP 1993 Measured concentrations 94–101% of target

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
Systemic									
28	Rat (F344) 5 M, 5 F	6 hr/d, 5 d/wk, up to 12 exposures in 16 d 0, 0.16, 0.5, 1.6, 5, 16 ppm (target)	BW CS GN LE OW	Resp BW	0.16 0.5	0.5	1.6	Exposure concentration-related increasing incidence and severity of respiratory tract lesions; body weight of 1.6 ppm rats approximately 40% less than that of controls	NTP 1993 Measured concentrations 96–100% of target
29	Rat (F344) 5 M, 5 F	6 hr/d, 5 d/wk for 6 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.125	0.25		Exposure concentration-related increasing incidence and severity of nasal lesions	Gross et al. 1994 Analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
30	Rat (F344) 5 M, 5 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.25	0.5		Exposure concentration-related increasing incidence and severity of nasal lesions	Gross et al. 1994 Analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
31	Rat (F344) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW	Resp Cardio Hemato Hepatic Renal BW	0.25 1.0 1.0 1.0 1.0 0.5 M 1.0 F	0.5 1.0M		Exposure concentration-related increasing incidence and severity of nasal lesions; body weight in 1.0 ppm males depressed by 10%; no histopathological evidence of cardiac lesions; increased numbers of segmented neutrophils at day 24; decreased numbers of leukocytes and lymphocytes at 13 weeks	NTP 1993 Measured concentrations 94–101% of target; no data regarding food consumption, which may have influenced body weight; changes in neutrophils likely secondary to nasal inflammation; changes in leukocytes and lymphocytes of small magnitude and questionable toxicological significance
32	Rat (F344) 20 M, 20 F	6 hr/d, 5 d/wk for 14 wk 0, 0.0208, 0.0493, 0.1942 ppm	BC BW CS FI GN HE HP LE OP OW	Resp Hemato Hepatic	0.1942 0.1942 0.1942			No evidence of exposure-related nasal or respiratory tract lesions or hematological effects	Union Carbide Corp 1992f
33	Mouse (B6C3F1) 5 M, 5 F	6 hr/d, 5 d/wk, up to 12 exposures in 16 d 0, 0.16, 0.5, 1.6, 5, 16 ppm (target)	BW CS GN LE OW	Resp BW	0.5 0.5	1.6		Exposure concentration-related increasing incidence and severity of respiratory tract lesions; body weights of 1.6, 5, and 16 ppm groups not measured due to 100% mortality in these groups	NTP 1993 Measured concentrations 94–101% of target

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
34	Mouse (Swiss OF1) 10 M	6 hr/d, 5 d/wk, for 14 exposures 0, 0.3, 0.9 ppm (measured)	BW CS GN HP	Resp		0.3		Exposure concentration-related increasing severity of nasal lesions	Zissu et al. 1994 Nasal lesions persisted for 2 wks in mice exposed at 0.9 ppm and observed for up to 4 wks after exposures ceased
35	Mouse (B6C3F1) 5 M, 5 F	6 hr/d, 5 d/wk for 6 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.125 M 0.0625 F	0.25 M 0.125 F		Exposure concentration-related increasing incidence and severity of nasal lesions	Gross et al. 1994 Analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
36	Mouse (B6C3F1) 5 M, 5 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	CS GN HP LE	Resp	0.0625 M	0.25 M 0.0625 F		Exposure concentration-related increasing incidence and severity of nasal lesions	Gross et al. 1994 Analytical concentrations within 99–104% of target (see Table 3-2 for quantitative nasal lesion data)
37	Mouse (B6C3F1) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW	Resp Cardio Hepatic Renal BW	0.25 M 0.5 0.5 0.5 0.25	0.5 M 0.0625 F[c] 0.5		Exposure concentration-related increasing incidence and severity of nasal lesions; no histopathological evidence of cardiac, liver, or renal lesions at highest nonlethal exposure level; 11–12% depressed body weight at 0.5 ppm	NTP 1993 Measured concentrations 94–101% of target; no data regarding food consumption, which may have influenced body weight
Neurological Effects									
38	Rat (F344) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW		1.0			No clinical signs of neurotoxicity	NTP 1993 Measured concentrations 94–101% of target
39	Mouse (B6C3F1) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW		1.0			No clinical signs of neurotoxicity	NTP 1993 Measured concentrations 94–101% of target
Reproductive Effects									
40	Rat (F344) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW		1.0			No effects on testicular weight, sperm morphology, vaginal cytology	NTP 1993 Measured concentrations 94–101% of target

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
41	Mouse (B6C3F1) 10 M, 10 F	6 hr/d, 5 d/wk for 13 wk 0, 0.0625, 0.125, 0.25, 0.5, 1.0 ppm (target)	BW BC CS GN HE HP LE OW		1.0 M 0.5 F			No effects on testicular weight, sperm morphology, vaginal cytology; females of 0.25 and 0.5 ppm groups spent slightly more time than controls in diestrus and estrus and less time in metestrus	NTP 1993 Measured concentrations 94–101% of target
CHRONIC EXPOSURE									
Death									
42	Rat (F344) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.25, 0.5, 0.75 ppm (target)	BW CS GN HP LE				0.5 F	Mean survival times among 0, 0.25, 0.5, and 0.75 ppm groups of female rats were 675, 671, 636, and 573 days, respectively; no significant differences in survival among groups of male rats	NTP 1999
Systemic									
43	Rat (F344) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.25, 0.5, 0.75 ppm (target)	BW CS GN HP LE	Resp Cardio Gastro Hemato Hepatic Renal Endocr BW	 0.75 0.75 0.75 0.75 0.75 0.75 0.75 M 0.5 F	0.25 0.75 F		Hyperplasia and inflammation in nasal squamous epithelium at all exposure levels; additional nasal lesions at two highest exposure levels No histopathological evidence of cardiac, gastrointestinal, hepatic, or renal lesions, or lesions in endocrine tissues examined (adrenal cortex, pancreas, pituitary, thyroid, parathyroid) Body weight in 0.75 ppm females depressed by 14%	NTP 1999 No data regarding food consumption, which may have influenced body weight
44	Mouse (B6C3F1) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.0625, 0.125, 0.0.25 ppm (target)	BW CS GN HP LE	Resp Cardio Gastro Hemato Hepatic Renal Endocr BW	0.125 M 0.25 0.25 0.25 0.25 0.25 0.25 0.25	0.25 M 0.0625 F		Squamous metaplasia in 0.25 ppm males; hyaline degeneration of respiratory epithelium in all groups of females and squamous metaplasia in 0.125 and 0.25 ppm females No histopathological evidence of cardiac, gastrointestinal, hepatic, or renal lesions, or lesions in endocrine tissues examined (adrenal cortex, pancreas, pituitary, thyroid, parathyroid)	NTP 1999 No glutaraldehyde exposure-related histopathologic lesions in cardiovascular, gastrointestinal, hepatic, renal, or endocrine tissues
Neurological Effects									
45	Rat (F344) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.25, 0.5, 0.75 ppm (target)	BW CS GN HP LE		0.75			No clinical or histopathological signs of glutaraldehyde-induced neurotoxicity	NTP 1999

Table 3-1. Levels of Significant Exposure to Glutaraldehyde – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Results	Reference/comments
46	Mouse (B6C3F1) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.0625, 0.125, 0.0.25 ppm (target)	BW CS GN HP LE		0.25			No clinical or histopathological signs of glutaraldehyde-induced neurotoxicity	NTP 1999
Reproductive Effects									
47	Rat (F344) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.25, 0.5, 0.75 ppm (target)	BW CS GN HP LE		0.75			No increased incidences of histopathological lesions in reproductive organs or tissues	NTP 1999
48	Mouse (B6C3F1) 50 M, 50 F	6 hr/d, 5 d/wk for 104 wk 0, 0.0625, 0.125, 0.0.25 ppm (target)	BW CS GN HP LE		0.25			No increased incidences of histopathological lesions in reproductive organs or tissues	NTP 1999

[a]The number corresponds to entries in Figures 3-1 and 3-2.
[b]Used to derive an acute-duration inhalation MRL of 0.001 ppm for glutaraldehyde, as described in detail in Appendix A. The concentration was adjusted from intermittent exposure (6 hours) to account for continuous exposure (6 hours/24 hours) and converted to a human equivalent concentration. An uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for human variability) was applied.
[c]Study results used to derive an intermediate-duration inhalation MRL of 0.00003 ppm ($3x10^{-5}$ ppm), as described in detail in Appendix A. Benchmark dose analysis was performed on incidence data for inflammation in the nasal vestibule/anterior nares of B6C3F1 female mice to select a point of departure, which was adjusted from intermittent exposure (6 hours/day, 5 days/week) to account for continuous exposure and converted to a human equivalent concentration. An uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for human variability) was applied.

BC = biochemistry; BW = body weight; Cardio = cardiovascular; CI = confidence interval; CS = clinical signs; d = day(s); Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GC = gas chromatography; GN = gross necropsy; HE = hematology; Hemato = hematology; HP = histopathology; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LE = lethality; M = male(s); min = minute(s); MRL = Minimal Risk Level; NS = not specified; OP = ophthalmology; OW = organ weight; RD_{50} = concentration resulting in a 50% reduction in respiratory rate; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Glutaraldehyde - Inhalation

Acute (≤ 14 days)

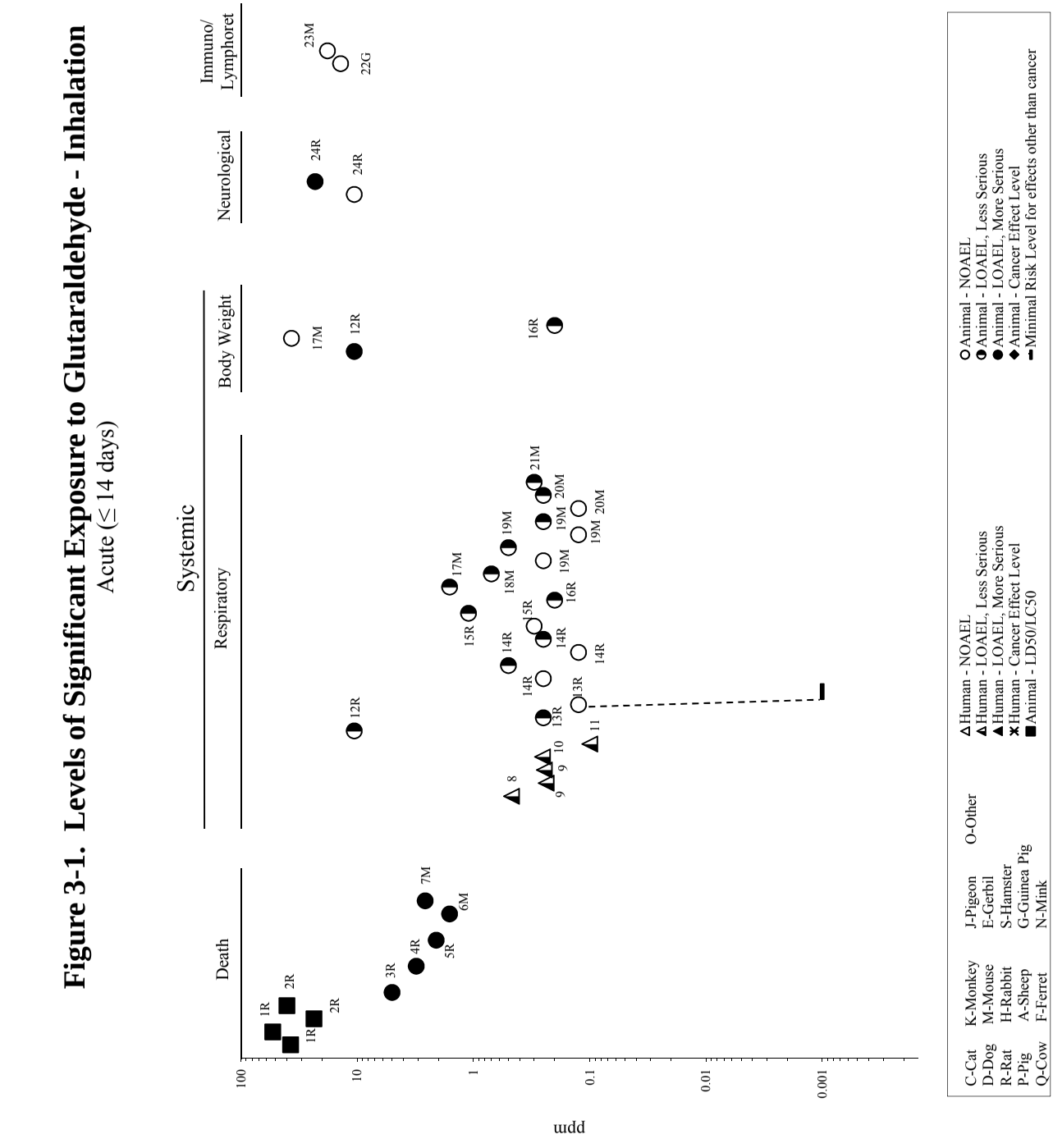


Figure 3-1. Levels of Significant Exposure to Glutaraldehyde - Inhalation *(Continued)*

Intermediate (15-364 days)

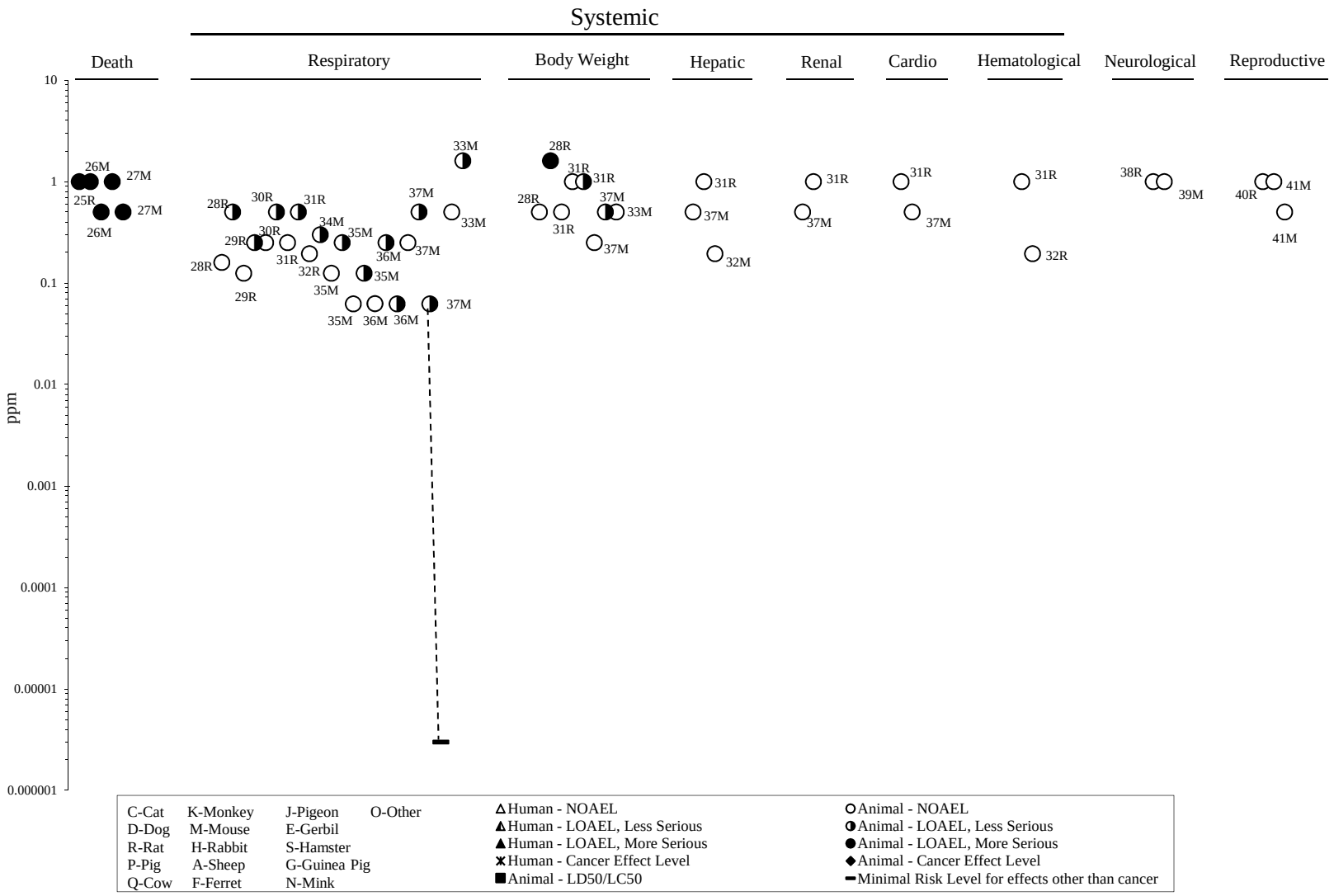


Figure 3-1. Levels of Significant Exposure to Glutaraldehyde - Inhalation *(Continued)*

Chronic (≥365 days)

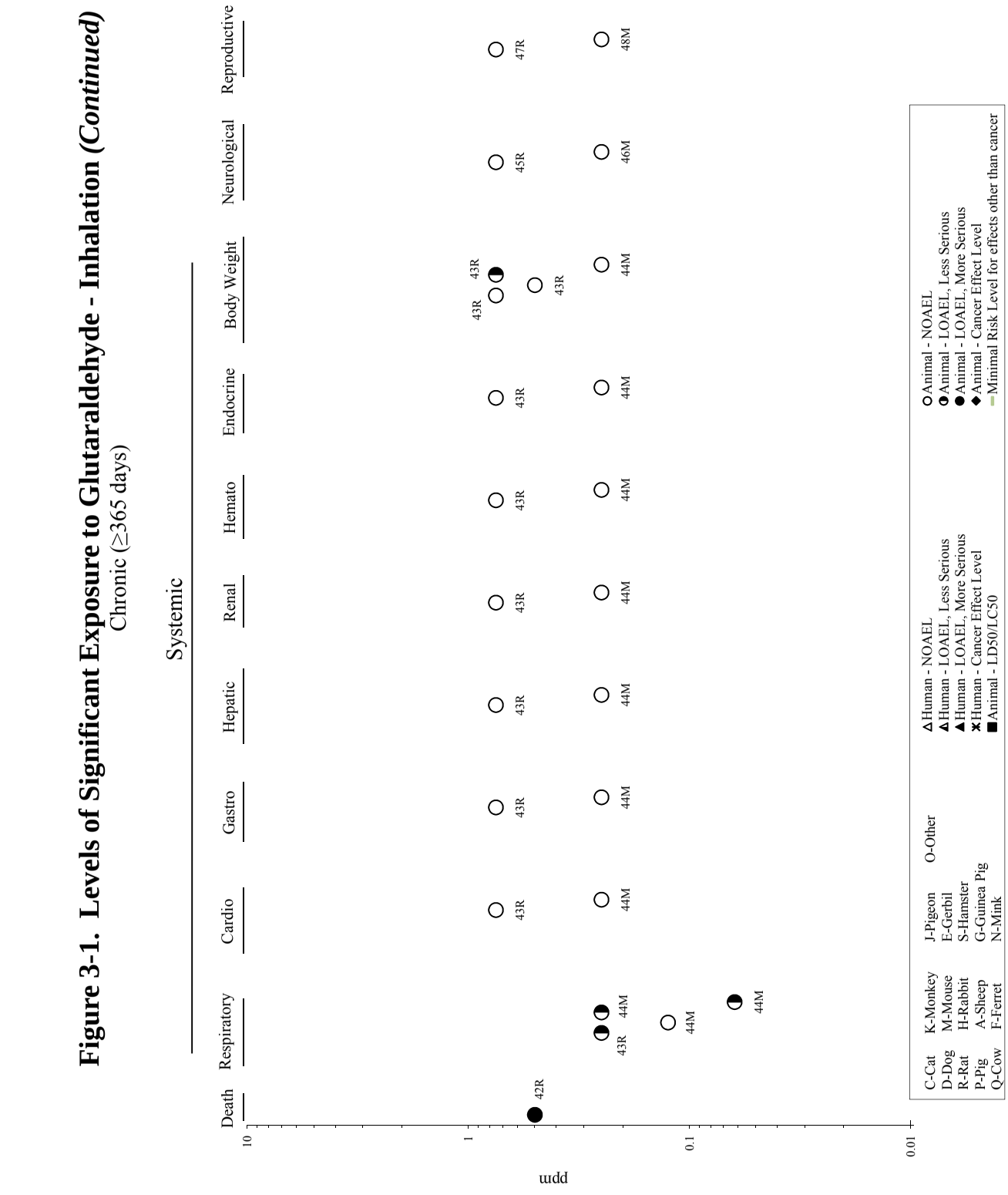


Table 3-2. Reported Respiratory Responses in Humans Exposed to Glutaraldehyde Vapor

Reference/subjects	Monitoring detail	Airborne concentration	Response
Union Carbide Corp. 1976 Controlled study: four female and five male volunteers exposed activated (alkaline) glutaraldehyde for 2-minute intervals over 3 days and unactivated (acidic) glutaraldehyde on a 4th day	Room air sampled for 30 minutes following exposures using air scrubber	Not specified in available study summary	Sensory (mainly nasal) irritation threshold of 0.237–0.245 ppm for alkaline glutaraldehyde, 0.255 ppm for acidic glutaraldehyde
Cain et al. 2007 Controlled study: 43 female subjects for odor detection (multiple 5-second exposures); 40 female subjects for nasal sensation (multiple 5-second exposures); 50 subjects for exposure duration assessment (multiple 15-minute exposures)	Sampling for odor detection: 2 L/minute over 30 minutes (limit of sensitivity: 0.00044 ppm) Sampling for nasal sensation: 15-minute measurements at sampling rate of 1 L/minute); limit of sensitivity: 0.0044 ppm	Multiple unspecified concentrations	Odor detection threshold: 0.0003 ppm (GSD=2.5) for 50% detection of odor Perception of nasal sensation: 0.470 ppm (GSD=1.6) for 50% detection of nasal sensation Exposure duration assessment: no convincing evidence of duration-related increased ability to detect a glutaraldehyde-induced nasal sensation during exposure (15 min at 0.035, 0.050, 0.075, or 0.100 ppm)
Norbäck 1988 Manual cold sterilization hospital workers: 39 exposed (handled glutaraldehyde ≥1 time/month); 68 unexposed (handled glutaraldehyde <1 time/month)	Personal monitoring: short-term (15 minutes) long-term (3–4 hours)	15 minutes: GM=0.05 mg/m^3 (0.012 ppm) range: <0.02–0.57 mg/m^3 (<0.0049–0.14 ppm) 3–4 hours: less than the detection limit of 0.04 mg/m^3 (<0.0098 ppm)	Nasal catarrh[a]: 26% exposed; 10% unexposed OR=3.0 (p=0.04) Nasal obstruction: 28% exposed; 12% unexposed OR=2.9 (p=0.03) Smarting of throat: 26% exposed; 9% unexposed OR=3.6 (p=0.02)

Table 3-2. Reported Respiratory Responses in Humans Exposed to Glutaraldehyde Vapor

Reference/subjects	Monitoring detail	Airborne concentration	Response
Vyas et al. 2000 Glutaraldehyde-exposed endoscopy nurses: 318 current workers; no comparison group	Personal monitoring of one nurse per endoscopy unit Background sampling (52 endoscopy units with 308 nurses) Peak glutaraldehyde sampling (43 endoscopy units with 267 nurses)	Peak[b]: GM=0.06 mg/m^3 (0.015 ppm); range <0.001 (LOD) to 1.08 mg/m^3 (<0.00024 ppm to 0.263 ppm) Background[c]: GM=0.01 mg/m^3 (0.0024 ppm); range 0.002–0.1 mg/m^3 (0.00049–0.024 ppm)	Nasal irritation reported by 63/318 (19.8%) workers with exposure to glutaraldehyde Significant association between peak glutaraldehyde concentration and prevalence of nasal irritation: RR=1.19 (95% CI 1.012, 1.402), adjusted for type of ventilation
Pisaniello et al. 1997 Nurses at 26 hospitals Exposed: 135 nurses with ≥1 year of experience with glutaraldehyde in endoscopy units and operating theaters Comparison group: 32 unexposed nurses at the same hospitals	Personal monitoring: short-term measurements (1–15 minutes) during glutaraldehyde use Area monitoring: unspecified duration (much longer than personal monitoring periods)	Short-term personal sampling: GM=0.032 ppm (GSD=3.0) Area sampling: GM=0.008 ppm (GSD=3.6)	At the end of a day of glutaraldehyde monitoring, 22/63 nurses (35%) reported any nasal symptoms, 8/63 (13%) reported any throat symptoms; no clear evidence of dose-response relationship (e.g., no symptoms associated with four personal monitoring measurements ≥0.2 ppm); significantly (p<0.05) higher prevalence of any throat symptom (occurring ≥3 times at work in last 12 months) in exposed (33/135; 24.4%) versus controls (13/132; 9.8%); no significant difference between exposed and controls regarding nasal symptoms

Table 3-2. Reported Respiratory Responses in Humans Exposed to Glutaraldehyde Vapor

Reference/subjects	Monitoring detail	Airborne concentration	Response
Waters et al. 2003 Glutaraldehyde-exposed subjects: 38 nurses from nine work areas (endoscopy units and operating theaters) at five health care facilities Comparison subjects: 38 workers (at two participating health care facilities) in areas where glutaraldehyde was not used	Breathing zone air samples collected during three main phases of disinfection (initial disinfection and immersion, removal and rinsing, and drying; mean duration 57, 142, and 90 seconds, respectively) Duration of designated exposure events: 5 seconds–12.25 minutes	Peak glutaraldehyde concentrations up to 0.15 ppm; lowest peak reading of 0.08 ppm where a washing machine was used	No significant association between exposure to glutaraldehyde and prevalence of nasal irritation, nasal burning, throat irritation, or cough
NIOSH 1987a 44 hospital workers exposed to glutaraldehyde at least once per week during disinfection of equipment	Five personal breathing zone samples and nine area samples (sampling times: 7–30 minutes at 0.8–1.0 L/minute flow rate)	Personal breathing zone samples: two ND, one each at 0.6 mg/m^3 (0.15 ppm), 0.8 mg/m^3 (0.20 ppm), and 1.6 mg/m^3 (0.39 ppm) Area samples: ND–1.0 mg/m^3 (0.24 ppm)	Nose irritation: 28/44 workers Throat irritation: 14/44 workers
NIOSH 1987b Unspecified number of nurses involved in disinfecting equipment and other contaminated surfaces at a medical facility	Eight personal breathing zone samples and nine area samples (sampling times: 15–45 minute at 0.2 L/minute flow rate)	Personal breathing zone samples: ND–1.98 mg/m^3 (0.48 ppm); 50% above 0.7 mg/m^3 (0.17 ppm); LOD=0.33–1.0 mg/m^3 (0.08–0.24 ppm) Area samples: ND–0.74 mg/m^3 (0.18 ppm)	Unspecified numbers of self-reported symptoms including nose and throat irritation during glutaraldehyde use

[a]Inflammation of mucous membrane, accompanied by excessive secretions.
[b]Period of biocide changeover (a relatively short time period when glutaraldehyde was replaced in sterilization equipment; personal sampler flow rate 1 L/minute).
[c]Glutaraldehyde concentration during a given endoscopy session (personal sampler flow rate of 200 mL/minute) minus the biocide changeover period.

CI = confidence interval; GM = geometric mean; GSD = geometric standard deviation; LOD = level of detection; ND = not detected; OR = odds ratio; RR = relative risk

concentration of 0.035 ppm to slightly more than 50% at 0.1 ppm (Cain et al. 2007). Nasal irritation was reported by human subjects exposed to glutaraldehyde vapor concentrations as low as 0.237 ppm for 2 minutes, which was considered the threshold for nasal irritation (Union Carbide Corp. 1976). 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 (e.g., Jachuck et al. 1989; NIOSH 1987a, 1987b; Norbäck 1988; Pisaniello et al. 1997; Vyas et al. 2000; Waldron 1992; Waters et al. 2003). 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 0.012–0.17 ppm (NIOSH 1987a, 1987b; Norbäck 1988; Pisaniello et al. 1997; Vyas et al. 2000). See Table 8-1 for information regarding occupational exposure limits for glutaraldehyde. Information regarding occupational exposure to glutaraldehyde and respiratory sensitization is discussed in Section 3.2.1.3 (Immunological and Lymphoreticular Effects).

Studies in animals identify the upper respiratory tract as a particularly sensitive target of glutaraldehyde toxicity following inhalation exposure. Single 4–8-hour exposure of rats to saturated atmospheres of glutaraldehyde vapor (generated at 21–25°C) resulted in clinical signs of respiratory tract irritation during exposure (Ballantyne 1995; Union Carbide Corp. 1992c, 1992d); although glutaraldehyde vapor concentrations were not monitored in these studies, they were likely <20 ppm. Single exposures of mice to glutaraldehyde vapor concentrations at 1.6–36.7 ppm for 30 minutes (Werley et al. 1995) or 0.7–4.3 ppm for 1 hour (Zissu et al. 1994) resulted in calculated 30-minute and 1-hour RD_{50} values of 13.86 and 2.6 ppm, respectively (RD_{50} is defined as the concentration resulting in a 50% reduction in respiratory rate). In rodents exposed to glutaraldehyde vapor for 4–6 hours/day and 1–14 exposures during 1–16 days, clinical signs of respiratory effects included nasal discharge, labored breathing, mouth breathing, audible respiration, rales, and perinasal encrustation at concentrations as low as 0.2–10.6 ppm (Ballantyne 1995; Gross et al. 1994; NTP 1993; Union Carbide Corp. 1992d, 1992e, 1992l; Zissu et al. 1994). Histopathologic evaluation of respiratory tissues revealed nasal lesions including rhinitis, epithelial changes (erosion, exfoliation, metaplasia), and mild atrophy of olfactory mucosa at exposure concentrations as low as 0.25–2.6 ppm (Gross et al. 1994; NTP 1993; Union Carbide Corp. 1992d; Zissu et al. 1994). Longer-term repeated exposures (6 weeks to 2 years) resulted in exposure concentration-related increased incidence and severity of clinical signs of respiratory irritation and histopathologic nasal lesions (exfoliation, inflammation, hyperplasia, and ulceration of nasal squamous epithelium; granulocytes and necrosis in nasal passages; laryngeal squamous metaplasia; necrosis in nasal nares) at exposure levels as low as 0.0625–1.0 ppm (Gross et al. 1994; NTP 1993, 1999; van Birgelen et al. 2000; Zissu et al. 1998). For example, nasal inflammation and neutrophilic infiltrate into nasal squamous

epithelium were observed in mice repeatedly exposed to glutaraldehyde vapor at 0.0625 ppm for 6 hours/day, 5 days/week, for 6 or 13 weeks (Gross et al. 1994; NTP 1993). Histopathologic nasal lesions were sometimes noted at exposure levels lower than those resulting in overt clinical signs of respiratory tract irritation.

The time-course of glutaraldehyde-induced nasal lesions was assessed in male and female F344/N rats and B6C3F1 mice exposed to glutaraldehyde vapor at 0.0625, 0.125, 0.25, 0.5, or 1 ppm for 6 hours/day for 1 or 4 days or 6 or 13 weeks (Gross et al. 1994; NTP 1993); results from the time-course study serve as basis for acute- and intermediate-duration inhalation MRLs for glutaraldehyde, as described in detail in Sections 2.3 and 3.6 and Appendix A. Groups of five animals/species/sex were evaluated at each time point; selected results for the rats and mice are summarized in Tables 3-3 and 3-4, respectively. All mice in the 1-ppm exposure group destined for evaluation at 6 and 13 weeks died or were sacrificed moribund prior to their scheduled sacrifice; deaths were attributed to chronic nasal obstruction and consequent asphyxiation. After a single exposure session, most rats and mice of the 0.5 and 1 ppm exposure levels exhibited layers of eosinophilic coagulated squames within the external nares that were apparently derived from exfoliation of squamous epithelial lining of the nasal vestibule and a mild neutrophilic infiltration in adjacent lamina propria. After four daily exposures at 0.5 or 1 ppm, the inflammatory response was more intense and many of the animals exhibited obstruction of the nasal passages with intraluminal debris. Extensive granulocytic intra- and subepithelial infiltration (principally neutrophils) was observed in the most anterior portion of the nasal vestibule of most 0.5- and 1-ppm mice and rats; however, interpretation of this lesion in the rats was complicated by the fact that most control and glutaraldehyde-exposed rats exhibited suppurative and nonsuppurative rhinitis. In general, neutrophilic infiltration increased in severity with time and exposure concentration in the time-course study and was most marked in all exposure groups of female mice at 13 weeks. The severity of neutrophilic infiltration in the rats appeared to peak at 6 weeks and decreased in severity at 13 weeks. Squamous metaplasia was observed in all 0.5- and 1-ppm male and female rats after four exposures and in most 0.5- and 1-ppm rats at the 6- and 13-week time points. However, although 4/5 of the 1-ppm male mice exhibited squamous metaplasia after four exposures, this lesion type was not as prominent at other time points or among the glutaraldehyde-exposed female mice. Other nasal lesions were generally confined to the higher exposure concentrations and included an array of degenerative and hyperplastic epithelial changes. Olfactory degeneration was noted in one or more 1-ppm male and female rats at all time points and in one or two 0.5-ppm male mice at 6 and 13 weeks. There was no evidence of glutaraldehyde-induced histopathologic lesions of lower respiratory tract regions in the rats and mice of the time-course study vapor concentrations as high as 1 ppm (Gross et al. 1994; NTP 1993). Discolored lungs were observed in some

Table 3-3. Incidences of Male and Female F344/N Rats with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 13 Weeks in the Time-Course Study

		Exposure level (ppm)[a]					
		0	0.0625	0.125	0.250	0.500	1.000
Male rats							
1 Day	Squamous exfoliation	0/5[b]	1/5	0/4	1/5	3/5	5/5
	Intraepithelial neutrophils	0/5	0/5	0/4	1/5 (0.4)[c]	2/5 (0.4)	5/5 (1.2)
	Subepithelial neutrophils	0/5	0/5	0/4	3/5 (0.8)	5/5 (1.8)	5/5 (2.6)
	Epithelial erosions	0/5	0/5	0/4	1/5	5/5	5/5
	Squamous metaplasia	0/5	0/5	0/4	3/5 (0.6)	1/5 (0.2)	1/5 (0.2)
4 Days	Squamous exfoliation	0/5	0/5	0/5	0/5	3/5	5/5
	Intraepithelial neutrophils	0/5	0/5	0/5	0/5	5/5 (1.4)	5/5 (2.6)
	Subepithelial neutrophils	1/5 (0.2)	0/5	2/5 (0.4)	1/5 (0.2)	5/5 (1.6)	5/5 (3.4)
	Epithelial erosions	0/5	0/5	0/5	1/5	2/5	5/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	5/5 (1.2)	5/5 (1.2)
6 Weeks	Squamous exfoliation	0/5	0/5	0/5	0/5	3/5	3/3
	Intraepithelial neutrophils	1/5 (0.2)	0/5	1/5 (0.2)	2/5 (0.4)	4/5 (0.8)	3/3 (3.0)
	Subepithelial neutrophils	2/5 (0.4)	3/5 (0.6)	2/5 (0.6)	4/5 (0.8)	5/5 (2.0)	3/3 (3.7)
	Epithelial erosions	0/5	0/5	0/5	0/5	4/5	3/3
	Squamous metaplasia	0/5	0/5	0/5	0/5	4/5 (1.6)	3/3 (3.3)
13 Weeks	Squamous exfoliation	0/5	0/5	0/5	2/5	2/5	2/5
	Intraepithelial neutrophils	5/5 (1.2)	3/5 (0.8)	5/5 (1.0)	5/5 (1.2)	4/5 (1.2)	5/5 (1.6)
	Subepithelial neutrophils	5/5 (1.0)	4/5 (1.0)	5/5 (1.2)	5/5 (1.6)	5/5 (1.4)	5/5 (2.0)
	Epithelial erosions	1/5	1/5	1/5	1/5	1/5	1/5
	Squamous metaplasia	1/5 (0.2)	0/5	0/5	0/5	5/5 (2.0)	5/5 (3.0)
Female rats							
1 Day	Squamous exfoliation	0/5	0/5	0/5	2/5	3/5	4/5
	Intraepithelial neutrophils	0/5	0/5	0/5	0/5	2/5 (0.6)	4/5 (1.0)
	Subepithelial neutrophils	0/5	0/5	1/5 (0.4)	1/5 (0.2)	5/5 (2.4)	5/5 (2.8)
	Epithelial erosions	0/5	0/5	1/5	0/5	4/5	5/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	0/5	0/5
4 Days	Squamous exfoliation	0/5	0/5	0/5	3/5	5/5	5/5
	Intraepithelial neutrophils	1/5 (0.2)	0/5	0/5	2/5 (0.4)	5/5 (2.2)	5/5 (3.4)
	Subepithelial neutrophils	2/5 (0.4)	0/5	0/5	4/5 (1.4)	5/5 (2.8)	5/5 (3.8)
	Epithelial erosions	0/5	0/5	0/5	2/5	3/5	5/5
	Squamous metaplasia	0/5	0/5	0/5	1/5 (0.2)	5/5 (2.0)	5/5 (3.0)

Table 3-3. Incidences of Male and Female F344/N Rats with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 13 Weeks in the Time-Course Study

		Exposure level (ppm)[a]					
		0	0.0625	0.125	0.250	0.500	1.000
6 Weeks	Squamous exfoliation	0/5	0/5	0/5	3/5	2/5	2/2
	Intraepithelial neutrophils	0/5	1/5 (0.2)	0/5	0/5	2/5 (0.6)	2/2 (3.5)
	Subepithelial neutrophils	1/5 (0.6)	2/5 (0.4)	1/5 (0.4)	1/5 (0.4)	5/5 (2.2)	2/2 (4.5)
	Epithelial erosions	0/5	0/5	0/5	0/5	4/5	1/2
	Squamous metaplasia	0/5	0/5	0/5	0/5	3/5 (0.6)	2/2 (3.5)
13 Weeks	Squamous exfoliation	0/5	0/5	0/5	0/5	2/5	4/4
	Intraepithelial neutrophils	1/5 (0.2)	0/5	1/5 (0.4)	3/5 (1.0)	2/5 (0.8)	4/5 (1.4)
	Subepithelial neutrophils	2/5 (0.4)	0/5	1/5 (0.8)	3/5 (1.0)	4/5 (1.8)	4/5 (2.0)
	Epithelial erosions	0/5	0/5	0/5	0/5	0/5	1/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	3/5 (1.2)	5/5 (2.6)

[a]Gray shaded cells suggest a glutaraldehyde-induced effect (lesion incidence at least 2 greater than controls).
[b]Incidence is the number of animals with lesions.
[c]Severity (in parentheses) was the mean for all animals in a group where: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

Sources: Gross et al. 1994; NTP 1993

Table 3-4. Incidences of Male and Female B6C3F1 Mice with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 13 Weeks in the Time-Course Study

		Exposure level (ppm)[a]					
		0	0.0625	0.125	0.250	0.500	1.000
Male mice							
1 Day	Squamous exfoliation	0/5[b]	0/5	0/5	0/5	4/5	5/5
	Intraepithelial neutrophils	1/5 (0.2)[c]	0/5	1/5 (0.2)	0/5	1/5 (0.2)	5/5 (1.0)
	Subepithelial neutrophils	1/5 (0.2)	0/5	1/5 (0.2)	1/5 (0.2)	2/5 (0.4)	5/5 (1.6)
	Epithelial erosions	0/5	0/5	0/5	0/5	1/5	2/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	0/5	0/5
4 Days	Squamous exfoliation	0/5	0/5	0/5	4/5	2/5	5/5
	Intraepithelial neutrophils	0/5	0/5	0/5	1/5 (0.2)	4/5 (1.8)	5/5 (2.8)
	Subepithelial neutrophils	0/5	0/5	0/5	2/5 (0.4)	4/5 (1.8)	5/5 (3.2)
	Epithelial erosions	0/5	0/5	0/5	0/5	1/5	2/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	1/5 (0.2)	4/5 (0.8)
6 Weeks	Squamous exfoliation	0/5	0/5	2/5	0/5	0/4	–[d]
	Intraepithelial neutrophils	0/5	0/5	0/5	1/5 (0.2)	1/4 (0.8)	–[d]
	Subepithelial neutrophils	0/5	0/5	0/5	1/5 (0.4)	4/4 (2.3)	–[d]
	Epithelial erosions	0/5	0/5	0/5	0/5	0/4	–[d]
	Squamous metaplasia	0/5	0/5	0/5	0/5	2/4 (0.5)	–[d]
13 Weeks	Squamous exfoliation	0/5	0/5	0/5	3/5	1/5	–[d]
	Intraepithelial neutrophils	0/5	0/5	1/5 (0.2)	4/5 (1.6)	5/5 (2.6)	–[d]
	Subepithelial neutrophils	0/5	1/5 (0.2)	2/5 (0.8)	5/5 (2.2)	5/5 (2.8)	–[d]
	Epithelial erosions	0/5	0/5	0/5	1/5	3/5	–[d]
	Squamous metaplasia	0/5	0/5	0/5	0/5	1/5 (0.2)	–[d]
Female mice							
1 Day	Squamous exfoliation	0/5	0/5	0/5	0/5	5/5	4/5
	Intraepithelial neutrophils	0/5	0/5	0/5	0/5	0/5	1/5 (0.4)
	Subepithelial neutrophils	0/5	0/5	1/5 (0.2)	0/5	2/5 (0.4)	3/5 (1.2)
	Epithelial erosions	0/5	0/5	0/5	0/5	0/5	1/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	0/5	0/5
4 Days	Squamous exfoliation	0/5	0/5	0/5	2/5	5/5	5/5
	Intraepithelial neutrophils	0/5	1/5 (0.2)	0/5	1/5 (0.4)	5/5 (1.0)	4/5 (0.8)
	Subepithelial neutrophils	0/5	0/5	0/5	1/5 (0.4)	5/5 (1.6)	5/5 (2.0)
	Epithelial erosions	0/5	0/5	0/5	0/5	0/5	2/5
	Squamous metaplasia	0/5	0/5	0/5	0/5	0/5	0/5

Table 3-4. Incidences of Male and Female B6C3F1 Mice with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 13 Weeks in the Time-Course Study

		Exposure level (ppm)[a]					
		0	0.0625	0.125	0.250	0.500	1.000
6 Weeks	Squamous exfoliation	0/5	0/5	0/5	0/5	2/5	–[d]
	Intraepithelial neutrophils	0/5	1/5 (0.4)	4/5 (1.6)	4/5 (1.8)	5/5 (2.2)	–[d]
	Subepithelial neutrophils	1/5 (0.2)	1/5 (0.4)	4/5 (2.0)	5/5 (2.4)	5/5 (2.6)	–[d]
	Epithelial erosions	0/5	0/5	0/5	0/5	0/5	–[d]
	Squamous metaplasia	0/5	0/5	0/5	0/5	3/5 (0.8)	–[d]
13 Weeks	Squamous exfoliation	0/5	05	0/5	0/5	1/4	–[d]
	Intraepithelial neutrophils	0/5	4/5 (2.0)	5/5 (2.4)	5/5 (3.2)	4/4 (2.8)	–[d]
	Subepithelial neutrophils	2/5 (0.4)	5/5 (2.0)	5/5 (2.8)	5/5 (3.2)	4/4 (2.8)	–[d]
	Epithelial erosions	0/5	0/5	0/5	0/5	0/4	–[d]
	Squamous metaplasia	0/5	0/5	0/5	0/5	1/4 (0.5)	–[d]

[a]Gray shaded cells suggest a glutaraldehyde-induced effect (lesion incidence at least 2 greater than controls).
[b]Incidence is the number of animals with lesions.
[c]Severity (in parentheses) was the mean for all animals within a group where: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[d]Not evaluated, all animals died.

Sources: Gross et al. 1994; NTP 1993

male and female rats following 4-hour exposure to glutaraldehyde vapor at 20 or 50 ppm (Union Carbide Corp. 1992l). Halatek et al. (2003) reported histopathologic lung lesions that included morphological changes in pulmonary epithelium of male rats exposed to glutaraldehyde vapor at 0.1 ppm, 6 hours/day, 5 days/week for 4 weeks. The study did not include evaluation of extrapulmonary respiratory tissues. Results from 13-week core studies of F344/N rats and B6C3F1 mice (NTP 1993) support the 13-week findings of the time-course study (Gross et al. 1994; NTP 1993). There was no histopathologic evidence of glutaraldehyde-induced lesions in the trachea or lungs of mice repeatedly exposed to glutaraldehyde vapor at up to 2.6 ppm for up to 14 days (Zissu et al. 1994) or other mice exposed at 0.1 ppm for up to 78 weeks (Zissu et al. 1998).

In 2-year chronic toxicity/carcinogenicity studies that employed exposure to glutaraldehyde vapor for 6 hours/day, 5 days/week, male and female F344/N rats (50/sex/group) were exposed at 0.25, 0.5, or 0.75 ppm and male and female B6C3F1 (50/sex/group) mice were exposed at 0.0625, 0.125, or 0.25 ppm (NTP 1999). Selected results for the rats and mice are summarized in Tables 3-5 and 3-6, respectively. Glutaraldehyde-related histopathological lesions were limited to the nasal cavity. Statistically significantly increased incidences of hyperplasia and inflammation within nasal squamous epithelium were observed in all groups of glutaraldehyde-exposed male and female rats, relative to controls. Hyperplasia and/or inflammation of the respiratory epithelium were observed in male and female rats of the two highest exposure concentrations (0.5 and 0.75 ppm). Other effects within the respiratory epithelium of both sexes of rats included significantly increased incidences of squamous metaplasia at 0.5 and 0.75 ppm and goblet cell hyperplasia at 0.75 ppm. Significantly increased incidences of hyaline degeneration within olfactory epithelium were noted in the 0.75-ppm male rats and 0.5- and 0.75-ppm female rats. Histopathologic nasal lesions among the mice exposed for 2 years included significantly increased incidences of squamous metaplasia of the respiratory epithelium of 0.25-ppm males and 0.125- and 0.25-ppm females, inflammation in the nasal cavity of 0.25-ppm females, and hyaline degeneration of respiratory epithelium in all glutaraldehyde-exposed groups of female mice. Histopathologic evaluations of pulmonary tissue from the rats and mice of the 2-year inhalation study revealed alveolar/bronchiolar adenoma in 1/50 of the 0.25- and 0.5-ppm males, 2/50 of the 0.75-ppm males, and 1/50 of the 0.5-ppm females (not statistically significantly different from control incidence of 0/50); the adenomas were not considered related to glutaraldehyde exposure. Statistically significantly increased incidences of histiocyte infiltration in 0.75-ppm females and interstitial fibrosis in 0.5- and 0.75-ppm females were not considered a direct effect of glutaraldehyde exposure because they are common spontaneous lesions in rats.

Table 3-5. Incidences of Male and Female F344/N Rats with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 2 Years

	Exposure level (ppm)			
	0	0.25	0.5	0.75
Male rats				
Squamous epithelium				
Hyperplasia	3/50 (2.0)[a]	11/50[b] (1.6)	39/50[c] (2.2)	48/50[c] (2.9)
Inflammation	6/50 (2.0)	17/50[b] (1.5)	41/50[c] (2.7)	49/50[c] (3.6)
Respiratory epithelium				
Hyperplasia	6/50 (2.0)	5/50 (2.0)	17/50[c] (1.9)	35/50[c] (1.9)
Inflammation	17/50 (2.1)	10/50 (1.5)	25/50 (2.4)	43/50[c] (3.2)
Squamous metaplasia	1/50 (2.0)	2/50 (1.5)	11/50[c] (2.0)	24/50[c] (2.2)
Goblet cell hyperplasia	1/50 (1.0)	0/50	6/50 (1.8)	6/50[b] (1.2)
Olfactory epithelium				
Hyaline degeneration	4/50 (1.0)	8/50 (1.3)	9/50 (1.1)	14/50[c] (1.1)
Female rats				
Squamous epithelium				
Hyperplasia	3/50 (1.3)	15/50[c] (1.7)	29/50[c] (2.0)	45/49[c] (2.7)
Inflammation	6/50 (2.5)	26/50[c] (1.5)	42/50[c] (2.1)	48/49[c] (3.2)
Respiratory epithelium				
Hyperplasia	1/50 (3.0)	6/50 (1.7)	15/50[c] (1.9)	29/49[c] (1.9)
Inflammation	5/50 (2.2)	9/50 (1.7)	26/50[c] (2.1)	42/49[c] (2.5)
Squamous metaplasia	1/50 (2.0)	1/50 (3.0)	11/50[c] (1.6)	16/49[c] (2.3)
Goblet cell hyperplasia	1/50 (2.0)	3/50 (1.3)	5/50 (1.4)	8/49[c] (1.6)
Olfactory epithelium				
Hyaline degeneration	4/50 (1.0)	5/50 (1.0)	12/50[b] (1.1)	15/49[c] (1.1)

[a]Severity (in parentheses) is the average grade of lesions in affected animals where: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly increased relative to chamber control group by the Poly-3 test ($p \leq 0.05$).
[c]Significantly increased relative to chamber control group by the Poly-3 test ($p \leq 0.01$).

Source: NTP 1999

Table 3-6. Incidences of Male and Female B6C3F1 Mice with Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for up to 2 Years

	Exposure level (ppm)			
	0	0.0625	0.125	0.25
Male mice				
Respiratory epithelium				
Squamous metaplasia	2/48 (1.0)[a]	5/50 (1.0)	6/50 (1.2)	9/50[b] (1.1)
Turbinate				
Necrosis	0/50	0/50	2/50 (2.0)	0/50
Female mice				
Inflammation	6/50 (1.2)	7/49 (1.3)	13/50 (1.4)	14/50[b] (1.4)
Respiratory epithelium				
Squamous metaplasia	7/50 (1.1)	11/49 (1.0)	16/50[b] (1.3)	21/50[c] (1.5)
Hyaline degeneration	16/50 (1.4)	35/49[c] (1.4)	32/50[c] (1.3)	30/50[b] (1.1)
Turbinate				
Necrosis	0/50	3/49 (2.0)	1/50 (1.0)	4/50 (1.5)

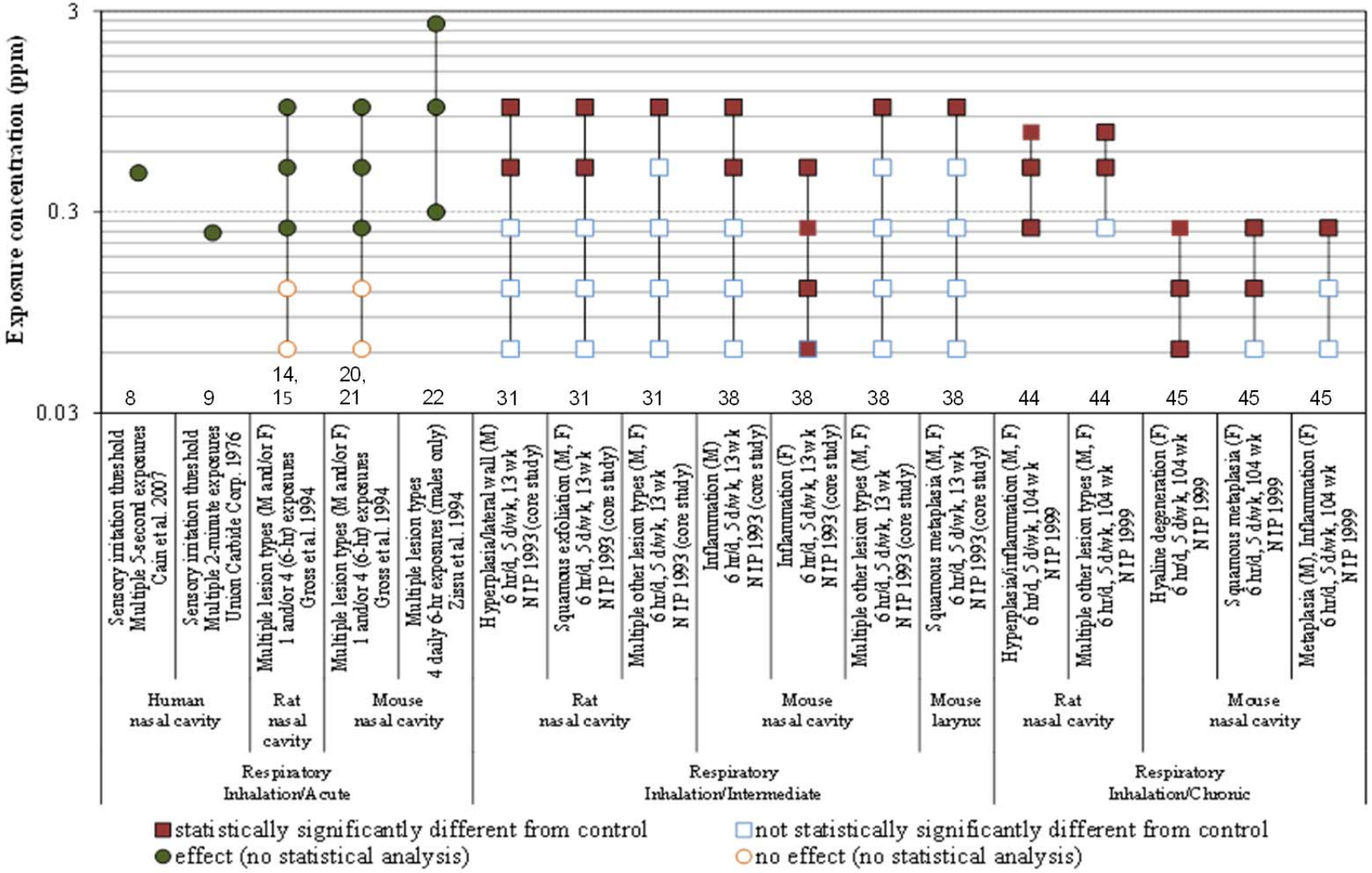
[a]Severity (in parentheses) is the average grade of lesions in affected animals where: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly increased relative to chamber control group by the Poly-3 test (p≤0.05).
[c]Significantly increased relative to chamber control group by the Poly-3 test (p≤0.01).

Source: NTP 1999

Selected results from acute-, intermediate- and chronic-duration inhalation exposure to glutaraldehyde in laboratory animals and controlled studies of humans are presented in Figure 3-2. Human nasal sensory irritation thresholds of 0.47 and 0.237 ppm for repeated 5-second or 2-minute inhalation exposures, respectively, are in the range of acute-duration exposure levels (0.25–0.5 ppm for 6-hour exposures during 1 or 4 days) for male and female rats and mice that elicited histopathologic nasal lesions (e.g., squamous exfoliation, infiltration of intra- and subepithelial neutrophils, epithelial erosions). Results of an NTP (1993) 13-week inhalation study (exposures of 6 hours/day, 5 days/week) of male and female rats and mice suggest that mice may be somewhat more susceptible to glutaraldehyde-induced nasal lesions than rats and that female mice may be more susceptible than male mice, as demonstrated by significantly increased incidence of nasal inflammation in the female mice at the lowest exposure level tested (0.0625 ppm) compared to a NOAEL of 0.25 ppm and a LOAEL of 0.5 ppm for nasal inflammation in the male mice. There was no indication of glutaraldehyde-induced nasal lesions in male or female rats exposed at 0.25 ppm; the 0.5 ppm level represented a LOAEL for male and female rats (squamous exfoliation in males and females, hyperplasia in respiratory epithelium of males). Multiple nasal lesion types (hyperplasia, squamous metaplasia, inflammation in respiratory epithelium, and squamous exfoliation in nasal vestibule/anterior nares of male and female rats; inflammation in respiratory epithelium, squamous exfoliation in nasal vestibule/anterior nares, squamous metaplasia in the larynx of male and female mice) were observed at the highest exposure level (1 ppm). Female mice also appeared to be the most sensitive to glutaraldehyde-induced nasal lesions following 2 years of repeated exposures (NTP 1999). The lowest exposure level tested (0.0625 ppm) resulted in respiratory epithelial hyaline degeneration in the female mice; squamous metaplasia was noted in the female mice of the next higher exposure level (0.125 ppm). A LOAEL of 0.25 ppm (the highest exposure level tested) was identified for squamous metaplasia in the male mice. In the male and female rats, the lowest exposure level tested (0.25 ppm) represented a LOAEL for hyperplasia and inflammation in squamous epithelium; the next higher exposure level for the rats (0.5 ppm) caused multiple other nasal lesion types (e.g., hyperplasia and squamous metaplasia in respiratory epithelium of male and female rats; inflammation in respiratory epithelium and hyaline degeneration in olfactory epithelium of female rats). The 2-year studies of rats and mice (NTP 1999) found no evidence of glutaraldehyde-induced neoplastic nasal lesions.

Cardiovascular Effects. Available information in humans is limited to a report from an occupational physician who had evaluated 7 separate cases of patients who presented with palpitations or tachycardia (Connaughton 1993). Occupational exposure was considered as a possible cause because the effects resolved when glutaraldehyde exposure ceased.

Figure 3-2. Exposure-Response Array of Selected Glutaraldehyde-Induced Respiratory Effects Following Acute-, Intermediate-, or Chronic-Duration Inhalation Exposure



There were no exposure-related effects on incidences of histopathologic lesions of the cardiovascular system of rats or mice following up to 2 years of repeated exposure to glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

Gastrointestinal Effects. There were no exposure-related effects on incidences of histopathologic lesions of the gastrointestinal system of rats or mice following up to 2 years of repeated exposure to glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

Hematological Effects. No exposure-related effects on hematological parameters were seen in rats exposed to glutaraldehyde vapor for 14 weeks (6 hours/day, 5 days/week) at 0.1942 ppm, the highest concentration tested (Ballantyne 1995; Union Carbide Corp. 1992f). A 13-week study of rats and mice exposed to glutaraldehyde vapor concentrations in the range of 0.0625–1 ppm included groups assigned for hematology and clinical chemistry evaluations at study days 4 and 24 (NTP 1993). Male rats from three of the four highest exposure groups and female rats from two of the three highest exposure groups exhibited significantly increased segmented neutrophils at day 24 assessment. Because the increase in segmented neutrophils was not accompanied by increased lymphocytes, the mature neutrophilia was considered the result of exposure-related inflammation in the nares and not a direct glutaraldehyde-induced hematological effect. Hematology results for core-study rats after 13 weeks of repeated exposure revealed significant changes in 0.5- and 1.0-ppm exposure groups of males that included decreased numbers of leukocytes (14 and 8%, respectively, lower than controls) and lymphocytes (16–17% lower than controls); however the changes in leukocyte and lymphocyte counts were apparently considered of little toxicological significance because there was no mention of these effects in the results or discussion sections of the study report. There were no exposure-related effects on incidences of histopathologic lesions in hematopoietic tissues of rats or mice following up to 2 years of repeated exposure to glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

Hepatic Effects. No exposure-related hepatic effects were seen in rats exposed to glutaraldehyde vapor for 14 weeks (6 hours/day, 5 days/week) at 0.1942 ppm, the highest concentration tested (Ballantyne 1995; Union Carbide Corp. 1992f). Varpela et al. (1971) reported toxic hepatitis in mice following inhalation of glutaraldehyde for 24 hours at a concentration of 0.133 mg/L (ca. 33 ppm). There were no exposure-related effects on incidences of histopathologic lesions of the liver of rats or mice following repeated exposure to glutaraldehyde for 13 weeks at vapor concentrations as high as 1 ppm

(rats) and 0.5 ppm (mice) (NTP 1993) or up to 2 years at vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

Renal Effects. No exposure-related renal effects were seen in rats exposed to glutaraldehyde vapor for 14 weeks (6 hours/day, 5 days/week) at 0.1942 ppm, the highest concentration tested (Ballantyne 1995; Union Carbide Corp. 1992f). There were no exposure-related effects on incidences of histopathologic renal lesions in rats or mice following repeated exposure to glutaraldehyde for 13 weeks at vapor concentrations as high as 1 ppm (rats) and 0.5 ppm (mice) (NTP 1993) or up to 2 years at vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

Endocrine Effects. There were no exposure-related effects on incidences of histopathologic lesions in endocrine organs or tissues (adrenal cortex, pancreas, pituitary, thyroid, parathyroid) in rats or mice following up to 2 years of repeated exposure of rats and mice to glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000). It should be noted that hormone levels were not monitored in these studies.

Ocular Effects. Occupational exposure to glutaraldehyde has been commonly associated with ocular irritation (Calder et al. 1992; Jachuck et al. 1989; NIOSH 1987a, 1987b; Pisaniello et al. 1997; Vyas et al. 2000; Waters et al. 2003). Refer to Section 3.2.3.2 (Ocular Effects) of this Toxicological Profile for Glutaraldehyde for additional information because the ocular effects were considered to have occurred as a result of direct ocular contact with airborne glutaraldehyde vapor.

Ocular results from studies in which laboratory animals were exposed to atmospheres containing glutaraldehyde vapor are summarized under dermal exposure because the effects resulted from direct contact with glutaraldehyde.

Body Weight Effects. Depressed body weight gain and actual body weight loss have been observed in laboratory animals exposed to glutaraldehyde vapor. Single exposure of male and female rats to glutaraldehyde vapor for 4 hours at analytical concentrations in the range of 9.1–43.5 ppm resulted in body weight loss ranging from 14 to 30% for up to 7 days postexposure and 35–42% depressed body weight gain over 14 days of postexposure observation (Union Carbide Corp. 1992l). Repeated 6-hour exposures of male and female rats to glutaraldehyde vapor (5/days/week for 11 days) resulted in 33–41% depressed body weight gain at 0.2 ppm glutaraldehyde and 21–22% body weight loss at 0.63 ppm (Union Carbide Corp. 1992e). Rats and mice repeatedly exposed to glutaraldehyde vapor at 0.9–1.6 ppm for

6 hours/day for periods of 12 days to 13 weeks exhibited significantly lower mean final body weights than their respective controls (NTP 1993; Zissu et al. 1994); as much as 41–42% lower final body weights were observed in male and female rats exposed to glutaraldehyde vapor at 1.6 ppm, 6 hours/day, for 12 exposures in a 16-day period (NTP 1993). In a 2-year repeated-exposure inhalation study, exposures of male and female rats to glutaraldehyde vapor at 0.75 ppm resulted in approximately 9 and 14% lower mean body weights, respectively (NTP 1999; van Birgelen et al. 2000).

3.2.1.3 Immunological and Lymphoreticular Effects

Case reports of some workers exposed to glutaraldehyde during disinfection processes provide some evidence of glutaraldehyde-induced respiratory hypersensitivity. Gannon et al. (1995) reported seven cases of workers from endoscopy or x-ray departments with occupational asthma (as determined by peak expiratory flow measurements and positive specific bronchial challenge tests to glutaraldehyde). The median airborne glutaraldehyde level at the time of challenge was 0.068 mg/m^3 (0.0166 ppm); the range was 0.064–0.081 mg/m^3 (0.0156–0.0198 ppm). To estimate occupational glutaraldehyde exposure levels, 30 personal air samples were taken from 13 hospital endoscopy units. Median glutaraldehyde concentrations were 0.016 mg/m^3 (95% confidence interval [CI] 0.12–0.68 mg/m^3) or 0.0039 ppm for short-term exposure during activities likely to produce peak levels of glutaraldehyde vapor, 0.041 mg/m^3 (95% CI 0.016–0.14 mg/m^3) or 0.01 ppm for long-term samples (34–120 minutes, during which time exposure was intermittent), and 0.17 mg/m^3 (95% CI 0.12–0.25 mg/m^3) or 0.0415 ppm for static short-term samples. Glutaraldehyde air concentrations in 19 air samples collected from 6 x-ray darkrooms were <0.009 mg/m^3 (<0.0022 ppm). The study did not include blood testing for antibodies or other signs of glutaraldehyde-induced allergy. Di Stefano et al. (1999) reported similar results for eight hospital workers with occupational asthma; glutaraldehyde challenge concentrations for those workers averaged 0.075 mg/m^3 (0.018 ppm). Other cases of glutaraldehyde-induced occupational asthma have been reported as well (Chan-Yeung et al. 1993; Corrado et al. 1986; Cullinan et al. 1992; Ong et al. 2004; Quirce et al. 1999; Trigg et al. 1992).

A single-blind placebo-controlled study of 11 health workers with diagnoses of glutaraldehyde-induced occupational asthma and rhinitis and occupational exposures to glutaraldehyde during 2–10 years, 10 nonexposed atopic subjects with perennial asthma and rhinitis, and 10 nonexposed healthy subjects was performed to evaluate changes in nasal lavage fluid content before and following glutaraldehyde challenge exposure (Palczyński et al. 2001). The mean airborne glutaraldehyde concentration during challenge was 0.32±0.08 mg/m^3 (0.077 ppm). Upon glutaraldehyde challenge, those subjects diagnosed

with occupational asthma exhibited significantly increased eosinophil numbers and percentages and significantly increased concentrations of albumin, eosinophil cation protein, and mast-cell tryptase in the nasal lavage fluid. These results are suggestive of an immunologic mechanism for glutaraldehyde-induced asthma. A similarly-designed study evaluated bronchoalveolar lavage fluid (BALF) components and Clara cell protein (CC16) concentration in serum and BALF before and after glutaraldehyde inhalation challenge (Palczyński et al. 2005). Postchallenge evaluation revealed significantly lower Clara cell protein levels in BALF and serum at 24 hours postchallenge and significant increases in proportions of eosinophils, basophils, and lymphocytes in BALF of the glutaraldehyde-sensitized asthmatics.

Other studies found no evidence of glutaraldehyde-induced respiratory sensitization. In a survey of 150 hospital workers with exposure to glutaraldehyde, symptoms of respiratory and ocular irritation were commonly reported, but there was no indication of allergic responses (Waldron 1992). Similar results were obtained in a survey of 348 nurses in endoscopy units of facilities in the United Kingdom and 18 former workers (Vyas et al. 2000). Waters et al. (2003) reported significant cross-shift reductions in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in a group of 38 glutaraldehyde-exposed nurses following work shifts during which short term airborne glutaraldehyde levels measuring up to 0.15 ppm were recorded; however, the mean decreases in FVC and FEV_1 were of small magnitude (<10%) and no significant differences were found regarding prevalence of self-reported respiratory irritation symptoms between exposed and unexposed workers.

There were no indications of glutaraldehyde-induced respiratory sensitization within a group of 218 workers employed at a glutaraldehyde production facility (Teta et al. 1995). The time period of assessment was 1959–1992. The average time spent in the glutaraldehyde production or drumming areas was 3.8 years and workplace time-weighted average (TWA) glutaraldehyde concentrations between 1977 and 1992 ranged from 0.04 to 0.08 ppm, except for 1982 (TWA of 1.02 ppm).

Limited information is available regarding the potential for inhaled glutaraldehyde to cause immunological effects in laboratory animals. Male Dunkin-Hartley guinea pigs were exposed to glutaraldehyde vapor at approximately 14 ppm for 1 hour/day for 5 consecutive days followed by 1-hour challenge exposures at approximately 4.4 ppm at 14, 21, and 35 days following the final induction exposure (Werley et al. 1995). There was no evidence of glutaraldehyde-induced respiratory sensitization. Exposure of BALB/c mice to glutaraldehyde vapor or aerosols at 6 or 18 ppm for 1.5 hours/day on 3 consecutive days resulted in clinical signs of respiratory tract irritation, but no

evidence of glutaraldehyde-induced respiratory sensitization as assessed by the local lymph node assay (LLNA) (van Triel et al. 2011).

3.2.1.4 Neurological Effects

Information regarding neurological effects in humans exposed to glutaraldehyde is limited to reports of increased incidences of self-reported headaches among occupationally-exposed workers during disinfection processes in which glutaraldehyde was used (e.g., Guthua et al. 2001; Norbäck 1988; Pisaniello et al. 1997; Waters et al. 2003).

Impaired righting reflex was noted in rats exposed to glutaraldehyde vapor at 42.7 ppm for 4 hours; decreased motor activity was observed during 14 days of postexposure observation at exposure concentrations of 23 and 42.7 ppm (Union Carbide Corp. 1992l). There were no clinical signs of neurotoxicity in male or female rats or mice exposed to glutaraldehyde vapor at concentrations as high as 1 ppm for 6 hours/day, 5 days/week for 13 weeks (NTP 1993) or rats or mice similarly exposed for up to 2 years at glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999). The 2-year study found no evidence of glutaraldehyde-induced neurohistopathological effects.

Katagiri et al. (2011) measured neurotransmitter levels in various brain regions of the rat following nose-only exposure to glutaraldehyde vapor for 1 hour/day, 5 days/week for 4 weeks at concentrations in the range of 50–200 ppb (0.05–0.2 ppm). In the medulla oblongata (the only region in which glutaraldehyde exposure-related changes were found), significantly lower mean 5-hydroxyindoleacetic acid content was observed at glutaraldehyde vapor concentrations of 0.05–0.2 ppm (20–30% lower than that of controls). Dopamine content was significantly lower at glutaraldehyde exposure concentrations of 0.1 and 0.2 ppm (20–38% lower than that of controls). The toxicological significance of the reported results is uncertain in the absence of obvious clinical signs of toxicity and lack of neurological histopathology other than monitoring of neurotransmitter levels. Other studies found no evidence of glutaraldehyde-induced neurotoxicity in laboratory animals repeatedly exposed to higher glutaraldehyde vapor concentrations for longer periods (NTP 1993, 1999).

3.2.1.5 Reproductive Effects

Rates of spontaneous abortion for the years 1951–1960, 1961–1970, and 1971–1981 were evaluated among sterilizing staff employed at Finnish hospitals and control workers at the same hospitals who were not occupationally exposed to sterilizing agents (Hemminki et al. 1982). Evaluation of those workers

exposed to glutaraldehyde (but not other sterilizing agents) during pregnancy (n=364) and those not exposed to glutaraldehyde or other sterilizing agents during pregnancy (n=768) revealed no significant differences in frequency of spontaneous abortion 9.4 versus 7.8% for controls) after adjusting for age, parity, decade of pregnancy, smoking habits, and alcohol and coffee consumption. Data obtained from hospital discharge registers that included details of spontaneous abortions among glutaraldehyde-exposed sterilizing staff (n=178) and controls (n=368) during the years 1973–1979 revealed rates of spontaneous abortions among the controls and glutaraldehyde-exposed staff of 9.2 and 12.9%, respectively (no statistically significant difference). Another study included nurses employed in selected departments at Finnish hospitals between 1973 and 1979 in which 217 cases of women with spontaneous abortions were compared to controls consisting of nurses with normal births and matched by age and employment facility (generally three controls per case) (Hemminki et al. 1985). The cases and controls had the potential for exposure to anesthetic gases, cytostatic drugs, and other hazardous substances including glutaraldehyde. One result of the study was the observation that similar proportions of spontaneous abortion cases and normal birth controls were exposed to glutaraldehyde (34/164 or 20.7% for cases and 88/464; 19.0% for controls). However, the small numbers of study subjects precludes any definitive conclusions regarding possible associations between exposure to glutaraldehyde and incidences of spontaneous abortions.

No animal studies specifically designed to assess the reproductive toxicity of inhaled glutaraldehyde were located. Evaluations of testicular weight, sperm morphology, and vaginal cytology in rats and mice exposed to glutaraldehyde vapor at concentrations in the range of 0.0625–1 ppm for 6 hours/day, 5 days/week for 13 weeks revealed no evidence of exposure-related adverse effects, although female mice of the two highest nonlethal exposure levels (0.25 and 0.5 ppm) spent significantly more time in estrous stages than controls ($p<0.05$) (NTP 1993). The toxicological significance of this finding and its potential human relevance are uncertain. No increased incidences of nonneoplastic lesions in reproductive organs or tissues were observed following 2 years of repeated exposure of rats and mice to glutaraldehyde vapor concentrations as high as 0.75 ppm (rats) and 0.25 ppm (mice) (NTP 1999; van Birgelen et al. 2000).

3.2.1.6 Developmental Effects

Available information regarding the potential for glutaraldehyde-induced developmental effects in humans is limited to results of a study that included nurses employed in selected departments at Finnish hospitals between 1973 and 1979 with 46 documented cases of mothers with a malformed child and controls consisting of nurses with normal births and matched by age and employment facility (generally three controls per case) (Hemminki et al. 1985). The cases and controls had the potential for exposure to

anesthetic gases, cytostatic drugs, and other hazardous substances including glutaraldehyde. One result of the study was the observation of similar proportions of glutaraldehyde-exposed mothers among the malformed child cases (5/34 or 14.7%) and the controls with normal births (17/95 or 17.9%). However, the small numbers of study subjects precludes any definitive conclusions.

No animal studies designed to assess the developmental toxicity of inhaled glutaraldehyde were located.

3.2.1.7 Cancer

Limited human data were located. Teta et al. (1995) found no evidence of increased mortality from cancer (total malignant neoplasms) within a group of 186 workers assigned to glutaraldehyde production or drumming from 1959 to 1992 at a West Virginia facility when compared to the general U.S. population. A total of 4 cancer deaths were observed compared to 6.1 expected (standardized mortality ratio [SMR] = 0.065; 95% CI 0.2–1.7). The cancer SMR was lower for those who worked ≥5 years in the units. Although the study authors associated the healthy worker effect with noncancer causes of death, there was no mention of such an effect for death due to cancer. Follow-up of this cohort resulted in no evidence for increased cancer rates for respiratory cancers (SMRs of 0.9 [95% CI 0.7–1.1], 1.0 [95% CI 0.2–3.0], and 0.3 [95% CI 0.0–1.5] for workers in categories of unexposed, >0–100 ppb-years, and 100+ ppb-years, respectively) or leukemia (0 cases among glutaraldehyde-exposed workers versus 0.6 expected) (Collins et al. 2006).

NTP determined that there was *no evidence of carcinogenic activity* of glutaraldehyde in male or female F344/N rats exposed to glutaraldehyde vapor at 250, 500, or 750 ppb or male or female B6C3F1 mice exposed to 62.5, 125, or 250 ppb for up to 2 years (NTP 1999). This determination was based on the lack of treatment-related increased incidences of neoplastic lesions in any organ or tissue from the rats or mice. Glutaraldehyde is not included in the list of agents evaluated for carcinogenicity by IARC (2013).

3.2.2 Oral Exposure

3.2.2.1 Death

Available human data are limited to a single case report of a 78-year-old man who deliberately ingested an unspecified quantity of a biocide containing glutaraldehyde and a quaternary ammonium compound (Simonenko et al. 2009). The man developed acute respiratory distress syndrome and severe metabolic acidosis 24 hours after being admitted to a hospital, and died 21 days after hospital admission.

The acute oral lethality of glutaraldehyde has been evaluated in laboratory animals using a variety of aqueous dilutions. For 50% aqueous glutaraldehyde, reported single-dose LD_{50} values fall within a range of 87–734 mg glutaraldehyde/kg for rats (Ballantyne 1995; BASF Corp 1990j; Union Carbide Chem & Plas Co. 1992; Union Carbide Corp. 1992b) and 115–151 mg glutaraldehyde/kg for mice (Ballantyne 1995; Union Carbide Corp. 1992i). Evaluations of glutaraldehyde dilution on acute lethality in male and female rats and mice indicate greater lethality at dilutions in the range of 1–15% compared to more concentrated solutions. For example, LD_{50} values of 734, 498, 166, 165, and 123 mg glutaraldehyde/kg were reported for male rats administered glutaraldehyde as 50, 25, 10, 5, or 1% aqueous glutaraldehyde, respectively (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991l). Similarly, LD_{50} values of 115, 228, 28.9, 29.7, and 14.8 mg glutaraldehyde/kg were reported for female mice administered 50, 25, 5, 1, or 0.1% aqueous glutaraldehyde, respectively (Ballantyne 1995; Union Carbide Corp. 1992i). However, expressed in terms of volume of glutaraldehyde per kg body weight, the LD_{50} values for these mice increased with increasing volume (e.g., 0.2, 0.81, 0.54, 2.83, and 13.5 mL/kg for 50, 25, 5, 1, and 0.1 mg glutaraldehyde/kg, respectively). In these studies, dosing volume varied for each concentration tested. Although underlying principles involved in the apparent increased lethality (in terms of mg glutaraldehyde/kg body weight) at lower glutaraldehyde concentrations have not been elucidated, these results indicate that administration of water following ingestion of relatively high concentrations of glutaraldehyde might enhance its toxicity. Stock glutaraldehyde is stored at relatively low pH (3.1–4.5) and is alkalinized to neutral pH (7.8–8.0) to optimize its biocidal activity as a disinfectant. In a study that evaluated the acute oral lethality of stock and alkalinized glutaraldehyde (2.2% aqueous solution), similar LD_{50} values were obtained for rats administered unbuffered or buffered solutions (Ballantyne 1995). LD_{50} values were 3.34 and 3.65 mL/kg (males) and 3.49 and 4.89 (females) for unbuffered and buffered solutions, respectively.

Maternal deaths were reported from daily gavage administration of 50% aqueous glutaraldehyde to rats during gestation days (GDs) 6–15 at 25 mg glutaraldehyde/kg (Ema et al. 1992) and rabbits during GDs 7–19 at 22.5 mg glutaraldehyde/kg (BASF Corp. 1991a). No treatment-related deaths were observed among rats, mice, or dogs administered glutaraldehyde in the drinking water for 13 weeks at concentrations resulting in ingested doses of glutaraldehyde as high as 120, 233, and 15 mg/kg/day, respectively (Union Carbide Chem & Plas Co. 1991r, 1991w, 1991ee). Continuous exposure of rats to glutaraldehyde in the drinking water for up to 2 years at concentrations resulting in glutaraldehyde doses as high as 64–121 mg/kg/day did not appear to affect survival (Confidential 2002; van Miller et al. 2002).

All reliable LOAEL and LD_{50} values for death in each species and duration category are recorded in Table 3-7 and plotted in Figure 3-3.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each species, duration, and end point for systemic effects are recorded in Table 3-7 and plotted in Figure 3-3.

No information was located regarding the following systemic effects in humans exposed to glutaraldehyde by the oral route: gastrointestinal, hematological, hepatic, renal, endocrine, body weight, and ocular effects. No information was located regarding the following systemic effects in laboratory animals exposed to glutaraldehyde by the oral route: cardiovascular, musculoskeletal, and dermal effects.

Respiratory Effects. Available human data are limited to two separate case reports. A 78-year-old male, who deliberately ingested an unspecified quantity of a biocide containing glutaraldehyde and a quaternary ammonium compound, developed acute respiratory distress and severe metabolic acidosis and subsequently died (Simonenko et al. 2009); the respiratory distress was likely secondary to metabolic acidosis. A 19-year-old female deliberately ingested an unspecified quantity of Omnicide (a poultry biocide containing 15% glutaraldehyde and 10% coco benzyl dimethyl ammonium chloride) (Perera et al. 2008). This subject also developed acute respiratory distress and severe metabolic acidosis, but subsequently recovered.

Gross pathologic evidence of glutaraldehyde-induced irritation in the lungs was observed following single gavage administration of aqueous glutaraldehyde to rats and mice at doses ≥100 and ≥16.9 mg/kg, respectively (Ballantyne 1995; Union Carbide Chem & Plas Co. 1992; Union Carbide Corp. 1992i). The respiratory effects are likely the result of aspiration of glutaraldehyde from the stomach. There were no indications of glutaraldehyde-induced respiratory effects in rats or mice receiving glutaraldehyde from the drinking water for 16 days or 13 weeks at doses as high as 100–120 mg/kg/day (rats) and 200–327.6 mg/kg/day (mice) (Union Carbide Chem & Plas Co. 1991r, 1991v, 1991w). In Wistar rats administered glutaraldehyde in the drinking water for up to 2 years at 2,000 ppm (estimated glutaraldehyde doses of 60 and 88 mg glutaraldehyde/kg for males and females, respectively), significantly increased incidences of nonneoplastic lesions were noted in larynx (diffuse squamous metaplasia in males and females and focal squamous metaplasia in females) and trachea (focal and diffuse squamous metaplasia in females) (BASF 2013; Confidential 2002). In addition, significant trends for

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
ACUTE EXPOSURE									
Death									
1	Rat (Wistar) 5 M, 5 F	Once (GW) 113, 170, 283, 565, 961	BW CS GN LE				181 M 209 F	LD_{50}=0.32 mL/kg (males), 0.37 mL/kg (females) for 50% aqueous glutaraldehyde	BASF Corp. 1990j Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
2	Rat (Wistar) 5 M	Once (GW) 283, 565, 1,130	BW CS GN LE					LD_{50}=1.3 mL/kg for 50% aqueous glutaraldehyde	Union Carbide Corp. 1992b Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
3	Rat (Sprague-Dawley) 5 M, 5 F	Once (GW) M: 50, 100, 200 F: 50, 70.5, 100	BW CS GN LE				139 M 87 F	LD_{50}=246 mg/kg (males), 154 mg/kg (females) for 50% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1992 Reported doses in mg test substance (50% aqueous glutaraldehyde/kg multiplied by 0.5 for expression as mg glutaraldehyde/kg
4	Rat (albino) 5 M	Once (GW) 252, 504, 1,008	BW CS GN LE		734			LD_{50}=1.19 mL/kg for 45% aqueous glutaraldehyde	Union Carbide Corp. 1992a Reported doses in mL/kg test substance (45% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.12 g/mL
5	Rat (Sprague-Dawley) 2 or 5 M, 2 or 5 F	Once (GW) 22.5, 45, 90, 180	BW CS GN LE		540		75.6 M 72.9 F	LD_{50}=168 mg/kg (males), 162 mg/kg (females) for 45% aqueous glutaraldehyde (Ucarcide antimicrobial 145LT)	Union Carbide Chem & Plas Co. 1991z Reported doses in mg test substance (45% aqueous glutaraldehyde)/kg multiplied by 0.45 for expression as mg glutaraldehyde/kg
6	Rat (Sprague-Dawley) 5 M, 5 F	Once (GW) M: 49, 99, 197, 394, 788 F: 99, 197, 394	BW CS GN LE				197 M 212 F	LD_{50}	Union Carbide Chem & Plas Co. 1991t Doses reported as mg active ingredient/kg; test substance was 45% aqueous glutaraldehyde
7	Rat (NS) NS	Once (GW) Doses NS	LE					Reported LD_{50}=1.54 mL/kg for 25% aqueous glutaraldehyde (dosed as received)	Union Carbide Chem & Plas Co. 1991g LD_{50} converted to mg/kg using specific gravity of 1.065 g/mL for 25% glutaraldehyde

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
8	Rat (Wistar) 5 M	Once (GW) 266, 533, 1,065	BW CS GN LE					LD_{50}=1.87 mL/kg for 25% aqueous glutaraldehyde	Union Carbide Corp. 1992c Reported doses in mL/kg test substance (25% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.065 g/mL
9	Rat (Hilltop-Wistar) 5 M, 5 F	Once (GW) 51, 103, 205, 410	BW CS GN LE		499		166 M 110 F	LD_{50}=1.62 mL/kg (males), 1.07 mL/kg (females) for 10% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991l Reported doses in mL/kg test substance (10% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.025 g/mL
10	Rat (Hilltop-Wistar) 5 M, 5 F	Once (GW) 51, 101, 203, 406, 811	BW CS GN LE				165 M 66 F	LD_{50}=3.25 mL/kg (males), 1.30 mL/kg (females) for 5% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991l Reported doses in mL/kg test substance (5% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.014 g/mL
11	Rat (Hilltop-Wistar) 5 M, 5 F	Once (GW) 40, 80, 160	BW CS GN LE				123 M 96 F	LD_{50}=12.3 mL/kg (males), 9.85 mL/kg (females) for 1% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991l Reported doses in mL/kg test substance (1% aqueous glutaraldehyde); converted to mg glutaraldehyde/kg using specific gravity of 1.0025 g/mL
12	Mouse (NS) 5 M, 5 F	Once (GW) M: 70.5, 141, 282 F: 70.5, 141, 282, 565	CS LE GN				151 M 115 F	LD_{50}	Union Carbide Corp. 1992i Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
13	Mouse (NS) 5 M, 5 F	Once (GW) M: 74.7, 149, 299, 598, 1,195 F: 149, 299, 598	CS LE GN				182 M 228 F	LD_{50}	Union Carbide Corp. 1992i Reported doses in mL/kg test substance (25% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.064 g/mL
14	Mouse (NS) 5 M, 5 F	Once (GW) M: 13.6, 27, 54, 109, 217, 434 F: 13.6, 27	CS LE GN				33.2 M 28.9 F	LD_{50}	Union Carbide Corp. 1992i Reported doses in mL/kg test substance (5% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.014 g/mL

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
15	Mouse (NS) 5 M, 5 F	Once (GW) M: 10.6, 21.2, 42.5 F: 5.3, 10.6, 21.2, 42.5, 85	CS LE GN				36.0 M 29.7 F	LD_{50}	Union Carbide Corp. 1992i Reported doses in mL/kg test substance (1% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.003 g/mL
16	Mouse (NS) 5 F	Once (GW) F: 4, 8, 16	CS LE GN				14.8	LD_{50}	Union Carbide Corp. 1992i Reported doses in mL/kg test substance (0.1% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.00 g/mL
17	Rat (Wistar) 21 or 26 F	1 x/d (GW) on Gd 6–15 0, 12.5, 25, 50	BW CS DX FI FX LE MX TG				25	12.5 mg/kg/d: no deaths 25 mg/kg/d: 2/21 maternal deaths 50 mg/kg/d: 5/26 maternal deaths	Ema et al. 1992 Reported doses in mg test substance/kg/d multiplied by 0.5 (proportion of glutaraldehyde in test substance) for expression as mg glutaraldehyde/kg/d
18	Rabbit (Himalayan) 15 F	1 x/d (GW) on Gd 7–19 0, 2.5, 7.5, 22.5	BW CS DX FI FX GN LE MX TG					2.5 mg/kg/d: no deaths 7.5 mg/kg/d: no deaths 22.5 mg/kg/d: 5/15 maternal deaths	BASF Corp 1991a Reported doses in mg test substance/kg/d multiplied by 0.5 (proportion of glutaraldehyde in test substance) for expression as mg glutaraldehyde/kg/d
Systemic									
19	Rat (Sprague-Dawley) 5 M, 5 F	Once (GW) M: 50, 100, 200 F: 50, 70.5, 100	BW CS GN LE	Gastro	50 M, F 22.5	100 M 70.5 F		Gastrointestinal irritation	Union Carbide Chem & Plas Co. 1992 Reported doses in mg test substance (50% aqueous glutaraldehyde/kg multiplied by 0.5 for expression as mg glutaraldehyde/kg. Discolored lungs at some dose levels were a likely result of aspiration.
20	Rat (Harlan-Wistar) 5 M	DW for 4 d 0, 440, 640	BW CS FI LE OW WI	Hepatic BW	640 640			Increased relative kidney weight, decreased urinary output at 440 and 640 mg/kg/d; no effects on relative liver weight or body weight	Union Carbide Chem & Plas Co. 1991f Kidney effects likely result of decreased food and water intake
21	Rat (Harlan-Wistar) 5 M	DW for 4 d 0, 180	BW CS FI LE OW WI	Hepatic Renal BW	180 180 180			No effects on relative liver or kidney weight or body weight	Union Carbide Chem & Plas Co. 1991f

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
22	Rat (Wistar) 10 F	1 x/d (GW) on Gd 6–15 0, 10, 50	BW CS DX FI FX LE MX TG WI	Gastro Hepatic Renal BW	10 50 10 50	50 50		50 mg/kg/d: thickened margo plicatus in forestomach of 10/10 dams, unspecified lesions in glandular stomach of 3/10 dams, 9% decreased serum total proteins, 10% increased mean relative kidney weight	BASF Corp. 1991b, 1991c Not specified whether reported doses were adjusted for proportion of glutaraldehyde in test substance (50% aqueous glutaraldehyde)
23	Rat (Wistar) 10 F	DW on Gd 6–16 0, 11, 51	BI BW CS DX FI FX GN HP LE MX OW TG WI	Gastro Hepatic Renal BW	11 51 51 51	51		Foci in glandular stomach of 2/10 dams	BASF Corp. 1990l, 1991b Author-estimated glutaraldehyde doses
24	Rat (Wistar) 25 F	DW on Gd 6–16 0, 5, 26, 68	BI BW CS DX FI FX GN HP LE MX OW TG WI	BW	68			No effects on mean maternal body weight	BASF Corp. 1991b Author-estimated glutaraldehyde doses
25	Rat (Wistar) 21 or 26 F	1 x/d (GW) on Gd 6–15 0, 12.5, 25, 50	BW CS DX FI FX LE MX TG	Gastro BW	25 25		50	50 mg/kg/d: hemorrhagic irritation of stomach noted in 12/21 dams; 57% depressed mean maternal body weight gain	Ema et al. 1992 Reported doses in mg test substance/kg/d multiplied by 0.5 (proportion of glutaraldehyde in test substance) for expression as mg glutaraldehyde/kg/d
26	Rat (F344) 10 M, 10 F	DW for 14 d M: 0, 12.8, 100.7 F: 0, 13.6, 105.5	BC BW CS FI GN HE HP LE WI	Hemato Hepatic Renal BW	100.7 M 105.5 F 100.7 M 105.5 F 100.7 M 105.5 F 100.7 M 105.5 F	50		No treatment-related effects on clinical signs, clinical chemistry or hematology measurements, body weight, absolute or relative liver or kidney weights, or histopathology of liver or kidney	Union Carbide Chem & Plas Co. 1991o Author-estimated glutaraldehyde doses
27	Mouse (NS) 5 M, 5 F	Once (GW) various doses	CS LE GN	Gastro	8.4	16.9		Gastrointestinal irritation	Union Carbide Corp. 1992i Results for 0.05% aqueous glutaraldehyde test substance; respiratory and gastrointestinal effects occurred at higher doses among mice treated using 0.1–50% aqueous glutaraldehyde test substance. Discolored lungs at some dose levels were a likely result of aspiration.
28	Rabbit (Himalayan) 6 F	DW on Gd 7–20 0, 7.1, 23.4	BW CS DX FI FX LE MX TG WI	Hepatic Renal BW	23.4 23.4 23.4			No effects on liver weight or gross lesions, kidney weight, or body weight	BASF Corp. 1991a, 1991c

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
29	Rabbit (Himalayan) 6 F	1 x/d (GW) on Gd 7–19 0, 5, 25	BW CS DX FI FX LE MX TG WI	Gastro Hepatic Renal BW	5 25 25 25	25		Gastritis in fundus/pyloris of 2/6 does, no treatment-related effects on liver, kidney, or body weights	BASF 1990m
30	Rabbit (Himalayan) 15 F	1 x/d (GW) on Gd 7–19 0, 5, 15, 45	BW CS DX FI FX GN LE MX TG	Gastro BW	15 15	 45	45	45 mg/kg/d: gastrointestinal irritative effects included reddening and ulceration in fundus, edema of fundus/ pylorus, distended cecum/colon in nearly all does; actual body weight loss during treatment period	BASF Corp. 1991a Body weight loss accompanied by 40% decreased food intake Note: 5/15 does in the 45 mg/kg/d group died
31	Dog (beagle) 2 M, 2 F	DW for 14 d M: 0, 7, 14 F: 0, 10, 13	BC BW CS FI GN HE HP LE OP UR WI	Gastro		7 M 10 F		Mucosal irritation (glossitis and esophagitis), more prominent in males	Union Carbide Chem & Plas Co. 1991dd Author-estimated glutaraldehyde doses
Developmental									
32	Rat (Wistar) 10 F	DW on Gd 6–16 0, 11, 51	BI BW CS DX FI FX GN HP LE MX OW TG WI		51			No effects on uterine weight or uterine contents	BASF Corp. 1990l, 1991b Author-estimated glutaraldehyde doses
33	Rat (Wistar) 10 F	1 x/d (GW) on Gd 6–15 0, 10, 50	BW CS DX FI FX LE MX TG WI		50			No effects on uterine weight or uterine contents	BASF Corp. 1991c Range-finding study for definitive study
34	Rat (Wistar) 25 F	DW on Gd 6–16 0, 5, 26, 68	BI BW CS DX FI FX GN HP LE MX OW TG WI		68			No effects on uterine weight or uterine contents	BASF Corp. 1991b Author-estimated glutaraldehyde doses
35	Rat (Wistar) 21 or 26 F	1 x/d (GW) on Gd 6–15 0, 12.5, 25, 50	BW CS DX FI FX LE MX TG		50			No effects on uterine weight or uterine contents up to and including maternally-toxic dose	Ema et al. 1992 Reported doses in mg test substance/kg/d multiplied by 0.5 (proportion of glutaraldehyde in test substance) for expression as mg glutaraldehyde/kg/d
36	Rabbit (Himalayan) 6 F	DW on Gd 7–20 0, 7.1, 23.4	BW CS DX FI FX LE MX TG WI		23.4				BASF Corp. 1991a, 1991c
37	Rabbit (Himalayan) 6 F	1 x/d (GW) on Gd 7–19 0, 5, 25	BW CS DX FI FX LE MX TG WI		25			No effect on fertility or fecundity	BASF 1990m

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
38	Rabbit (Himalayan) 15 F	1 x/d (GW) on Gd 7–19 0, 5, 15, 45	BW CS DX FI FX GN LE MX TG		15			45 mg/kg/d: decreased gravid uterine weight, decreased number of does with fetuses, 100% resorptions in 9/15 does, increased postimplantation loss, markedly reduced mean placental and fetal body weights	BASF Corp. 1991a Note: 45 mg/kg/d dose was extremely toxic; 5/15 does in the 45 mg/kg/d group died
INTERMEDIATE EXPOSURE									
Systemic									
39	Mouse (CD-1) 10 M, 10 F	DW for 16 d M: 0, 32.1, 69.8, 257.4 F: 0, 37.8, 92.5, 327.6	BC BW CS FI GN HE HP LE OW UR WI	Resp Hemato Renal BW	257.4 M 327.6 F 257.4 M 327.6 F 257.4 M 95.2 F 32.1 M 327.6 F	 327.6 F	 69.8 M	12% increased mean relative kidney weight in high-dose females; 32–77% depressed mean body weight gain in mid- and high-dose males	Union Carbide Chem & Plas Co. 1991v Author-estimated glutaraldehyde doses No histopathological evidence of treatment-related effects on kidney
40	Rat (F344) 20 M, 20 F	DW for 13 wk M: 0, 5, 23, 100 F: 0, 7, 35, 120	BC BW CS FI GN HE HP LE OP OW UR WI	Resp Hemato Hepatic Renal BW Ocular	100 M 120 F 100 M 120 F 100 M 120 F 5 M 7 F 100 M 120 F 100 M 120 F	 23 M 35 F		Dose-related increased absolute and/or relative kidney weight	Union Carbide Chem & Plas Co. 1991r Author-estimated doses No histopathological evidence of treatment-related effects on kidney

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
41	Mouse (CD-1) 20 M, 20 F	DW for 13 wk M: 0, 25, 61, 200 F: 0, 31, 74, 233	BC BW CS FI GN HE HP LE OP OW UR WI	Resp	200 M 233 F			Renal effects included decreased urine volume in males at 61 and 200 mg/kg/d and females at 233 mg/kg/d, increased mean urine osmolality in males at 61 and 200 mg/kg/d (~37% greater than controls) and females at 233 mg/kg/d (49% greater than controls	Union Carbide Chem & Plas Co. 1991w Author-estimated doses No histopathological evidence of treatment-related effects on kidney
				Hemato	200 M 233 F				
				Hepatic	200 M 233 F				
				Renal	25 M 74 F	61 M 233 F			
				BW	200 M 233 F				
				Ocular	200 M 233 F				
42	Rat (CD) 28 M (F0, F1) 28 F (F0, F1)	DW during premating, mating, gestation, and lactation for 2 generations F0 M: 0, 4.25, 17.5, 69.07 F0 F: 0, 6.68, 28.28, 98.37 F1 M: 0, 4.53, 21.95, 71.08 F1 F: 0, 6.72, 29.57, 99.56	BW CS DX FI FX GN HP LE MX TG WI	BW	69.07 F0 M 71.08 F1 M 98.37 F0 F 99.56 F1 F			F0 males: reduced body weight gain in mid- and high-dose groups only during first exposure week; decreased water consumption in mid- and high-dose groups; sporadic decreased food consumption in mid- and high-dose groups F0 females: reduced body weight gain in high-dose group only at weeks 3 and at parturition; decreased water consumption in mid- and high-dose groups; sporadic decreased food consumption in high-dose group F1 males: depressed body weight in high-dose group at times during premating only; decreased water consumption in mid- and high-dose groups; decreased food consumption in high-dose group F1 females: decreased water and food consumption in mid- and high-dose groups	Neeper-Bradley and Ballantyne 2000 Author-estimated doses Differences in body weight between controls and high-dose groups of parental rats were in the range of 5–6%, with the exception of 10 and 14% lower mean body weight of mid- and high-dose F0 male rats, respectively, at exposure week 1 No histopathological evidence of treatment-related effects on reproductive organs or tissues

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
43	Dog (beagle) 4 M, 4 F	DW for 13 wk M: 0, 3.3, 9.6, 14.1 F: 0, 3.2, 9.9, 15.1	BW BC BW CS FI GN HE HP LE OP OW UR WI	Gastro Hemato Hepatic Renal Ocular BW	3.3 M 3.2 F 14.1 M 15.1 F 14.1 M 15.1 F 14.1 M 15.1 F 14.1 M 15.1 F 14.1 M 15.1 F	9.6 M 9.9 F		Increased incidences of intermittent vomiting in mid- and high-dose males and females; reduced body weight and body weight gain in all dose groups of females (irregular intervals, small magnitude, and without dose-response characteristic); ophthalmologic examinations negative; increased relative kidney weight in high-dose females not considered biologically significant in absence of exposure-related changes in urinalysis or renal histopathology; no exposure-related effects on hematology, serum chemistry, or gross or histopathology	Union Carbide Chem & Plas Co. 1991ee Author-estimated doses
Reproductive									
44	Rat (CD) 28 M (F0, F1) 28 F (F0, F1)	DW during premating, mating, gestation, and lactation for 2 generations F0 M: 0, 4.25, 17.5, 69.07 F0 F: 0, 6.68, 28.28, 98.37 F1 M: 0, 4.53, 21.95, 71.08 F1 F: 0, 6.72, 29.57, 99.56	BW CS DX FI FX GN HP LE MX TG WI		69.07 F0 M 71.08 F1 M 98.37 F0 F 99.56 F1 F			No effects on fertility; no histopathological evidence of treatment-related effects on reproductive organs or tissues	Neeper-Bradley and Ballantyne 2000 Author-estimated doses

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
Developmental									
45	Rat (CD) 28 M (F0, F1) 28 F (F0, F1)	DW during premating, mating, gestation, lactation for 2 generations F0 M: 0, 4.25, 17.5, 69.07 F0 F: 0, 6.68, 28.28, 98.37 F1 M: 0, 4.53, 21.95, 71.08 F1 F: 0, 6.72, 29.57, 99.56	BW CS DX FI FX GN HP LE MX TG WI		98.37 F1 99.56 F2			F1 pups: significantly depressed mean pup body weight in high-dose pups at postpartum days 21 and 28 (5–11% lower than controls) and mean pup body weight gain during lactation days 14–28 (14–19% less than controls) F2 pups: significantly depressed mean pup body weight in high-dose pups at postpartum days 21 and 28 (7–13% lower than controls) and mean pup body weight gain during lactation days 14–28 (17–27% less than controls) No treatment-related effects on other developmental indices	Neeper-Bradley and Ballantyne 2000 Author-estimated doses Effects on pup body weight likely due to taste aversion
CHRONIC EXPOSURE									
Systemic									
46	Rat (F344) 100 M 100 F	DW up to 104 wk M: 0, 4, 17, 64 F: 0, 6, 25, 86	BC BW CS FI GN HE HP LE OP OW UR WI	Gastro Hemato Hepatic Renal BW	4 M[b] 6 F 64 M 86 F 64 M 86 F 64 M F 86 17 M 25 F	17 M 25 F 64 M 86 F		Gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa) in mid- and high-dose males and females; increased incidences of nucleated red blood cell and large monocytes in mid- and high-dose males and bone marrow hyperplasia in high-dose males and low-, mid-, and high-dose females; increased incidences of renal tubular pigmentation in high-dose males and mid- and high-dose females; increased kidney weight in high-dose females; decreased urine volume in high-dose males and females; depressed body weight and body weight gain in high-dose males and females (3–14% less than controls)	van Miller et al. 2002 Author-estimated doses Study authors considered most kidney effects a physiological compensatory adaptation to decreased water consumption and bone marrow hyperplasia, renal tubular pigmentation, and increased incidences of nucleated red blood cells and large monocytes secondary to low-grade anemia in rats with large granular lymphocytic anemia

Table 3-7. Levels of Significant Exposure to Glutaraldehyde – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ dose (mg/kg/d)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference/comments
47	Rat (Wistar) 50 M 50 F	DW up to 24 mo M: 0, 3, 16, 60 F: 0, 5, 24, 88	BC BW CS FI GN HE HP LE OP OW WI	Resp Gastro	16 M 24 F 60 M 24 F	60 M 88 F 88 F		Laryngeal and tracheal metaplasia in males and females; erosion/ulceration in glandular stomach of females	BASF 2013; Confidential 2002 A detailed study report is not available to the general public

[a]The number corresponds to entries in Figure 3-3.
[b]Used to derive a chronic-duration oral MRL of 0.1 mg/kg/day for glutaraldehyde. The NOAEL of 4 mg/kg/day was divided by an uncertainty factor of 30 (10 for extrapolation from animals to humans and 3 for human variability) (see Appendix A).

BC = biochemistry; BI = biochemical changes; BW = body weight; CS = clinical signs; d = day(s); DW = drinking water; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; Gd = gestation day(s); GN = gross necropsy; GW = gavage in water; HE = hematology; Hemato = hematological; HP = histopathology; LD_{50} = lethal dose, 50% kill; LE = lethality; M = male(s); MRL = Minimal Risk Level; MX = maternal toxicity; NS = not specified; OP = ophthalmology; OW = organ weight; Resp = respiratory; sec = second(s); TG = teratogenicity; UR = urinalysis; WI = water intake; wk = week(s); x = time(s)

Figure 3-3. Levels of Significant Exposure to Glutaraldehyde - Oral

Acute (≤ 14 days)

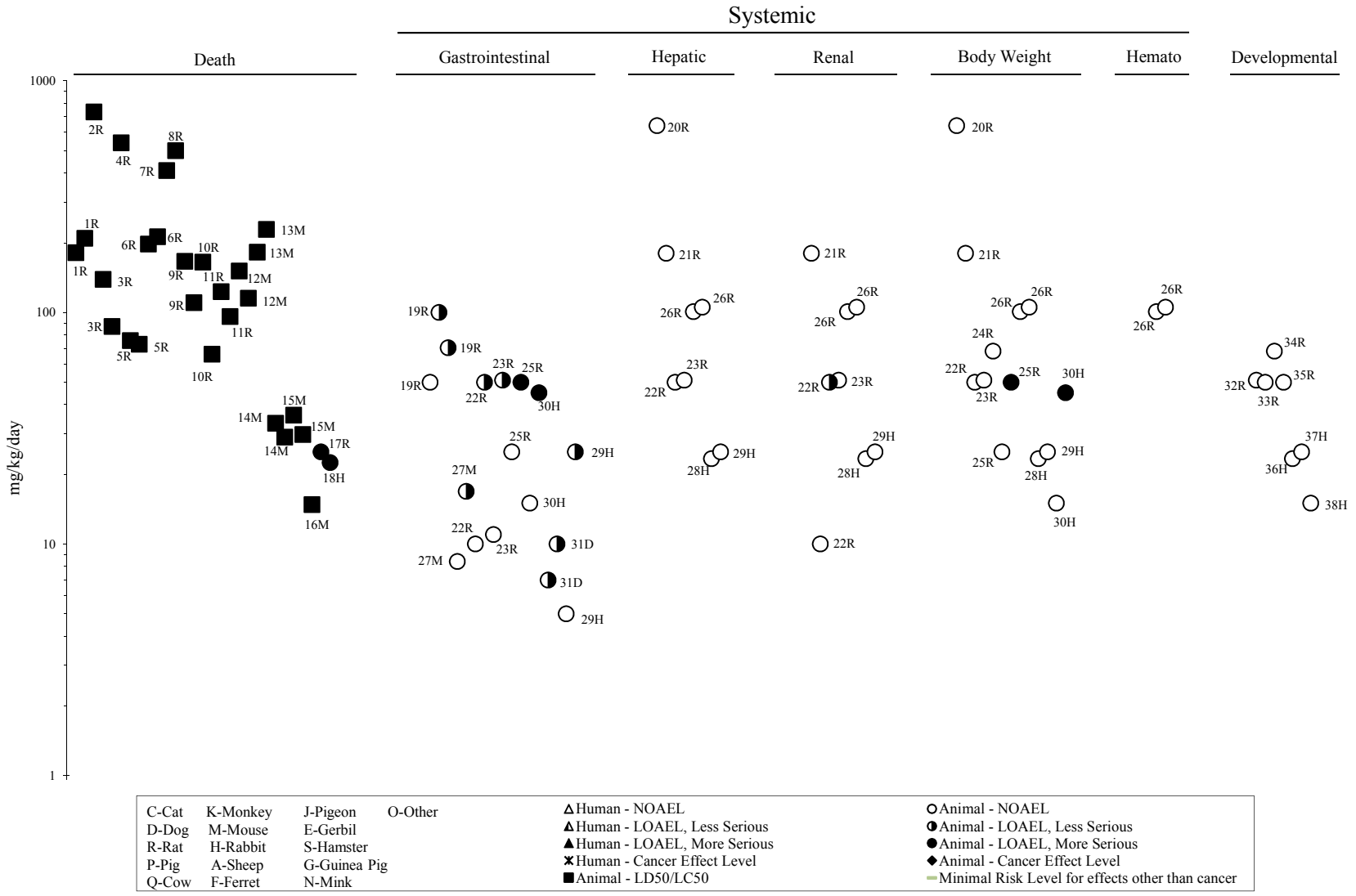


Figure 3-3. Levels of Significant Exposure to Glutaraldehyde - Oral *(Continued)*

Intermediate (15-364 days)

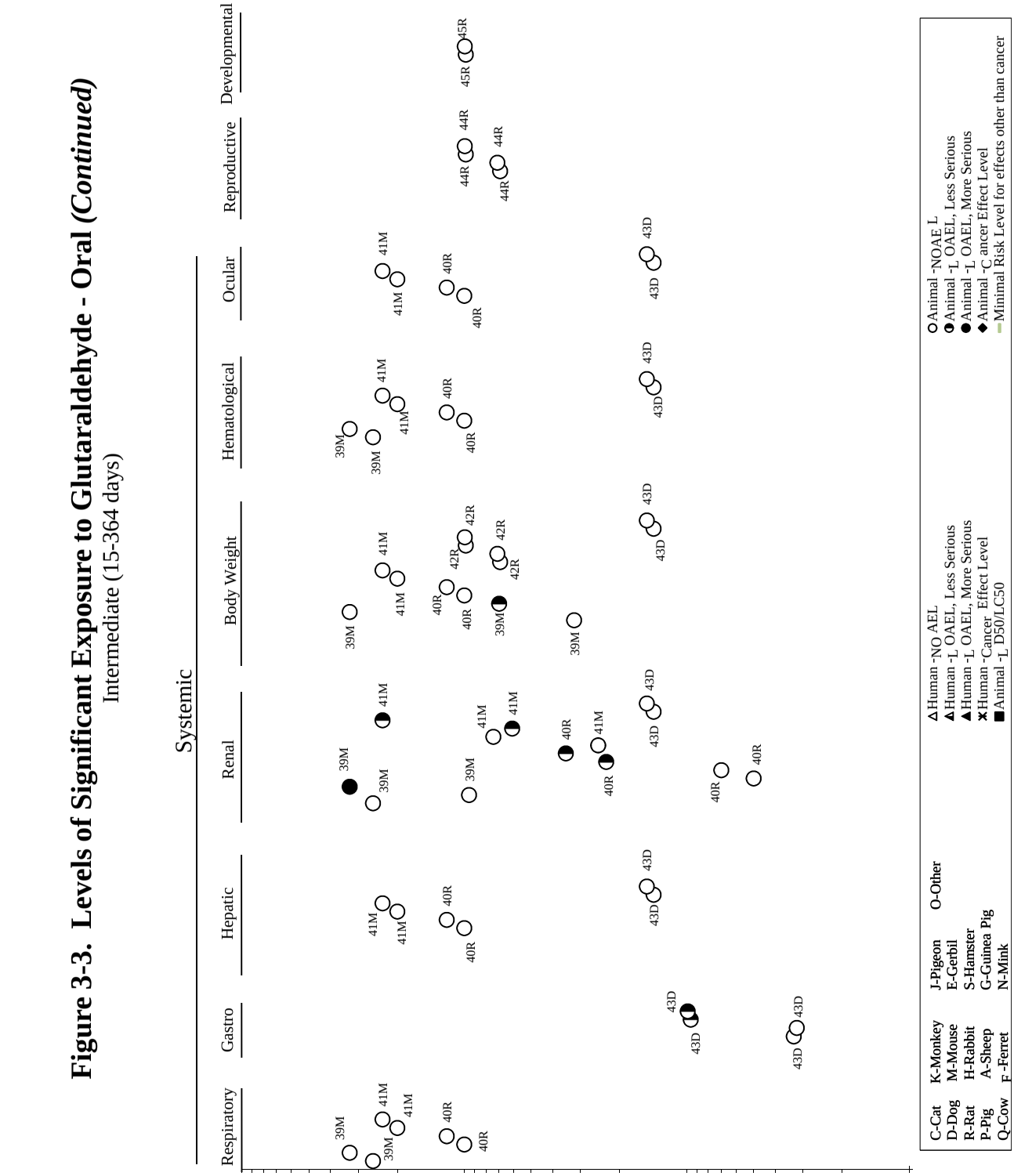
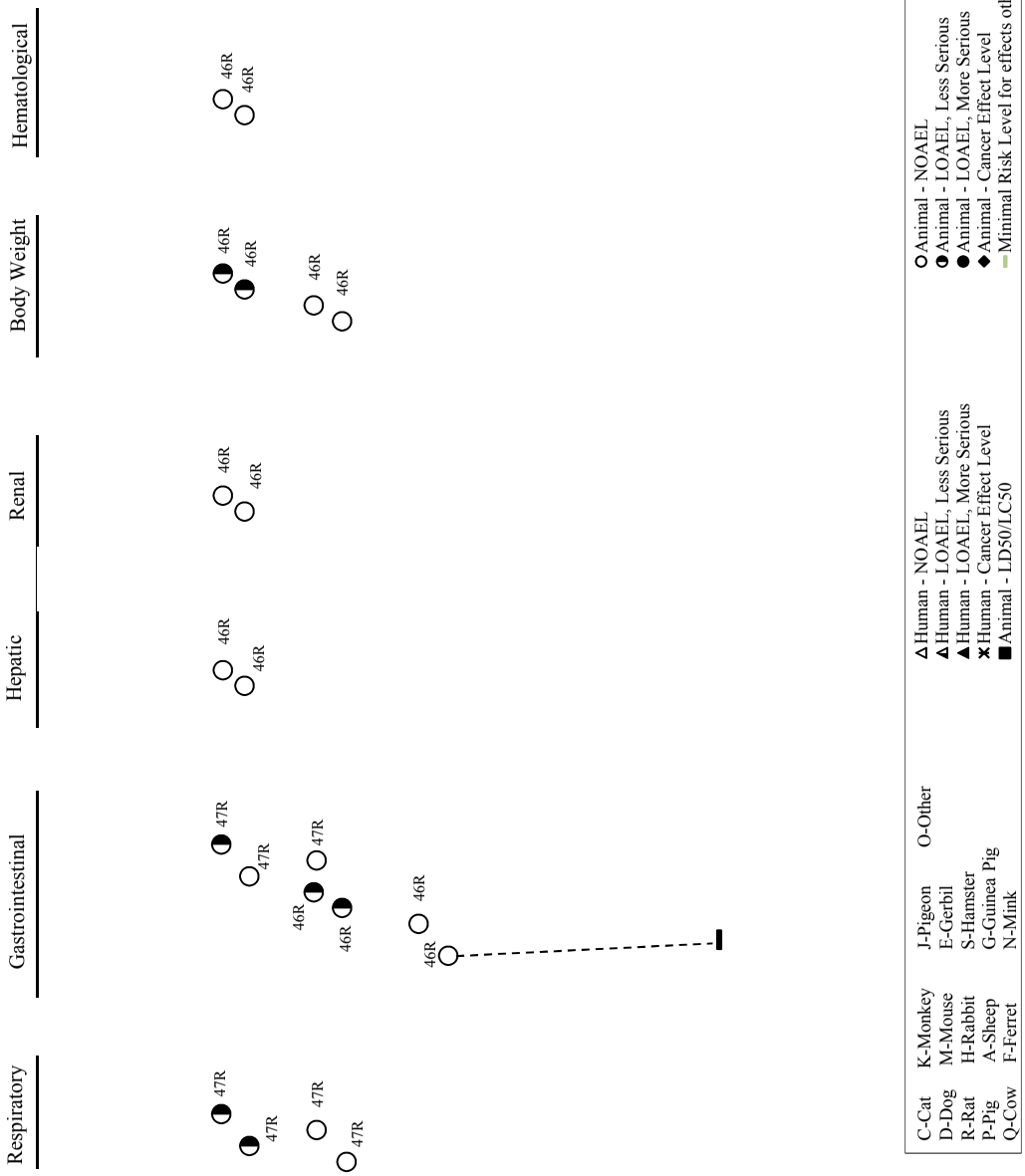


Figure 3-3. Levels of Significant Exposure to Glutaraldehyde - Oral *(Continued)*

Chronic (≥365 days)



increasing incidence with increasing glutaraldehyde concentration were noted for diffuse metaplasia in the larynx of male and female rats, focal metaplasia in the larynx of females, focal squamous metaplasia in the trachea of males and females, and diffuse metaplasia in the trachea of females.

Gastrointestinal Effects. Pathologic evidence of glutaraldehyde-induced gastrointestinal irritation was observed following administration of aqueous glutaraldehyde by single gavage at sublethal and lethal doses to rats and mice (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991t, 1991z, 1992; Union Carbide Corp. 1992a, 1992c, 1992i). Clinical signs of gastrointestinal disturbances (lack of fecal production, diarrhea, and bleeding) were noted in pregnant rabbits administered glutaraldehyde by gavage at 45 mg/kg/day during GDs 7–19 (BASF Corp. 1991a). Evidence of gastric irritation (e.g., thickened margo plicatus in the forestomach and unspecified lesions in the glandular stomach) were observed in pregnant Wistar rats administered glutaraldehyde by gavage at 50 mg/kg/day during GDs 6–15 (BASF Corp. 1991c; Ema et al. 1992). However, no clinical or gross pathologic signs of glutaraldehyde-induced gastrointestinal effects were observed in rat dams administered glutaraldehyde in the drinking water during GDs 6–16 at concentrations resulting in glutaraldehyde doses as high as 68 mg/kg/day (BASF Corp. 1991b). van Miller et al. (2002) reported gross and histopathological evidence of gastric irritation in nonglandular stomach mucosa of male and female rats receiving glutaraldehyde from the drinking water for 1–2 years at concentrations resulting in estimated glutaraldehyde doses of 17 and 64 mg/kg/day (males) and 25 and 86 mg/kg/day (females). These effects were not observed at estimated doses of 4 and 6 mg/kg/day to the males and females, respectively. In Wistar rats administered glutaraldehyde in the drinking water for up to 2 years at 2,000 ppm (estimated glutaraldehyde doses of 60 and 88 mg/kg for males and females, respectively), significantly increased incidence of erosion/ulceration was noted in the glandular stomach of the females (BASF 2013; Confidential 2002). Upper alimentary mucosal irritation was reported for dogs receiving glutaraldehyde from the drinking water for 14 days at 7–10 mg/kg/day (Union Carbide Chem & Plas Co. 1991dd). Vomiting was noted in male and female dogs receiving glutaraldehyde from the drinking water for 13 weeks at approximately 10 mg/kg/day; there was no indication of glutaraldehyde treatment-related vomiting in low-dose (ca. 3 mg/kg/day) dogs (Union Carbide Chem & Plas Co. 1991ee).

Hematological Effects. No treatment-related effects on hematology parameters were observed in studies of rats, mice, or dogs receiving glutaraldehyde from the drinking water for 2–13 weeks at doses as high as 100–120, 200–328, and 13–15 mg/kg/day, respectively (Union Carbide Chem & Plas Co. 1991o, 1991r, 1991v, 1991w, 1991ee). Significantly increased mean (±standard deviation [SD]) numbers of large monocytes were reported in the peripheral blood of male rats receiving glutaraldehyde from the

drinking water for up to 2 years at 17 or 64 mg/kg/day (5,761 per µL blood ± 17,648 and 6,984 per µL blood ± 24,262, versus 1,166 per µL blood ± 5,215 for controls) (van Miller et al. 2002). However, the toxicological significance of the increased numbers of large monocytes in the glutaraldehyde-exposed rats is uncertain because SDs were >3-fold higher than the mean, and increased numbers of peripheral blood nucleated erythrocytes and large monocytes are likely precursors to the development of LGLL, which occurs at high incidence in aged Fischer 344 rats (van Miller et al. 2002). In the same 2-year study, high incidences of bone marrow hyperplasia were observed in rats that died prior to terminal sacrifice as well as those surviving to terminal sacrifice; however, the bone marrow hyperplasia (along with renal tubular pigmentation) was considered most likely related to low-grade hemolytic anemia that accompanied LGLL in these rats (Stromberg et al. 1983; van Miller et al. 2002).

Hepatic Effects. Available animal studies provide no evidence of glutaraldehyde-induced hepatic effects following oral exposure for acute, intermediate, or chronic durations (BASF Corp. 1990l, 1990m, 1991c; Union Carbide Chem & Plas Co. 1991o, 1991r, 1991w, 1991dd, 1991ee; van Miller et al. 2002).

Renal Effects. Most animal studies provide no evidence of glutaraldehyde-induced renal effects following oral exposure for acute, intermediate, or chronic durations (BASF Corp. 1990l, 1990m, 1991c; Union Carbide Chem & Plas Co. 1991o, 1991r, 1991w, 1991dd, 1991ee). Increased relative kidney weight and decreased urinary output were observed in male Harlan-Wistar rats administered glutaraldehyde in the drinking water for 4 days at concentrations resulting in estimated doses of 440 and 640 mg/kg/day; however, the kidney effects were likely related to decreased food and water intake (Union Carbide Chem & Plas Co. 1991f). Significantly increased mean relative kidney weight (10% higher than controls) was noted in one study of rat dams administered glutaraldehyde by daily gavage on GDs 6–15 at 50 mg/kg/day (BASF Corp. 1991c); however, there was no effect on kidney weight in rat dams receiving glutaraldehyde from the drinking water during GDs 6–16 at 50 mg/kg/day (BASF Corp. 1990l). Approximately 12% increased mean relative kidney weight (in the absence of histopathologic renal lesions) was reported in female rats receiving glutaraldehyde from the drinking water for 16 days at 328 mg/kg/day; kidney weight was not affected in male rats similarly treated at up to 257 mg/kg/day (Union Carbide Chem & Plas Co. 1991v). Dose-related increased absolute and/or relative kidney weights were noted in F344 rats administered glutaraldehyde in the drinking water for 13 weeks at concentrations resulting in author-estimated glutaraldehyde doses of 23 mg/kg/day to the males and 35 mg/kg/day to the females (Union Carbide Chem & Plas Co. 1991r). In a study of CD-1 mice administered glutaraldehyde in the drinking water for 13 weeks, estimated glutaraldehyde doses of 23 and 100 mg/kg/day (males) and 120 mg/kg/day (females) resulted in decreased urine volume output and increased mean urine osmolality

in the absence of histopathological evidence of treatment-related histopathological kidney effects (Union Carbide Chem & Plas Co. 1991w). Renal tubular pigmentation was observed in glutaraldehyde-exposed male and female rats that died during chronic treatment in the drinking water at concentrations resulting in glutaraldehyde doses in the range of 4–86 mg/kg/day and in rats surviving until terminal sacrifice (van Miller et al. 2002); however, the pigmentation was considered most likely related to low grade hemolytic anemia that accompanied LGLL in these rats (Stromberg et al. 1983; van Miller et al. 2002).

Endocrine Effects. Information regarding endocrine effects in animals following oral exposure to glutaraldehyde is limited to reports that oral exposure for intermediate or chronic durations did not affect weights of adrenal gland, thyroid, ovaries, or testes (Union Carbide Chem & Plas Co. 1991r, 1991v, 1991w, 1991ee; van Miller et al. 2002).

Body Weight Effects. Significantly depressed mean maternal body weight gain (57% less than controls) was observed in rat dams administered aqueous glutaraldehyde at 50 mg/kg/day during GDs 6–15 (Ema et al. 1992). As much as 19% mean maternal body weight loss was reported in pregnant rabbits administered aqueous glutaraldehyde by gavage during GDs 7–19 at 45 mg/kg/day (BASF Corp. 1991a). No treatment-related effects on body weight were seen in male or female rats administered glutaraldehyde in the drinking water for 14 days at concentrations resulting in doses as high as 100–105 mg glutaraldehyde/kg/day (Union Carbide Chem & Plas Co. 1991o) or for 13 weeks at concentrations resulting in doses as high as 25–35 mg/kg/day (Union Carbide Chem & Plas Co. 1991r). Depressed body weight gain in male and female rats receiving glutaraldehyde from the drinking water at 100–120 mg/kg/day for 13 weeks was the likely result of decreased water and food consumption (Union Carbide Chem & Plas Co. 1991r). There were no treatment-related effects on mean body weight among female mice receiving glutaraldehyde from the drinking water for 16 days at doses up to 327 mg/kg/day; however, at doses ≥69.8 mg/kg/day, the males exhibited significantly depressed mean body weight gain (33–77% less than controls) (Union Carbide Chem & Plas Co. 1991v). In 13-week drinking water studies, no signs of treatment-related body weight effects were seen among male and female mice at glutaraldehyde doses as high as 200–233 mg/kg/day (Union Carbide Chem & Plas Co. 1991w) or male or female dogs at doses as high as 14–15 mg/kg/day (Union Carbide Chem & Plas Co. 1991ee). In a 2-year study of glutaraldehyde in the drinking water of rats, slightly (significant) depressed mean body weight and body weight gain were observed at glutaraldehyde doses of 64 mg/kg/day in males and 86 mg/kg/day in females; however, the rats exhibited significantly decreased water consumption as well (van Miller et al. 2002).

Ocular Effects. Available information regarding ocular effects in animals following oral exposure to glutaraldehyde consists of results from ophthalmologic evaluations. No signs of ocular effects were seen in rats, mice, or dogs receiving glutaraldehyde from the drinking water for 13 weeks at doses as high as 100–120, 257–327, and 14–15 mg/kg/day, respectively (Union Carbide Chem & Plas Co. 1991r, 1991v, 1991ee) or in rats receiving glutaraldehyde from the drinking water for 2 years at 64–86 mg/kg/day (van Miller et al. 2002).

Metabolic Effects. Available information regarding metabolic effects following oral exposure to glutaraldehyde is limited. Severe metabolic acidosis occurred in a 19-year-old female who deliberately ingested an unspecified quantity of Omnicide (a poultry biocide containing 15% glutaraldehyde and 10% coco benzyl dimethyl ammonium chloride) (Perera et al. 2008). A 78-year-old male, who deliberately ingested an unspecified quantity of a biocide containing glutaraldehyde and a quaternary ammonium compound, developed severe metabolic acidosis and acute respiratory distress and subsequently died (Simonenko et al. 2009).

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological or lymphoreticular effects in humans or laboratory animals following oral exposure to glutaraldehyde.

3.2.2.4 Neurological Effects

No information was located regarding neurological effects in humans or laboratory animals following oral exposure to glutaraldehyde.

3.2.2.5 Reproductive Effects

No data were located regarding reproductive effects in humans following oral exposure to glutaraldehyde.

Neeper-Bradley and Ballantyne (2000) exposed groups of parental (F0) male and female CD rats to glutaraldehyde in the drinking water at concentrations of 0, 50, 250, or 1,000 ppm glutaraldehyde during premating, mating, gestation, and lactation. Selected male and female pups (F1) were similarly-exposed through production of F2 pups that were maintained throughout lactation. Average glutaraldehyde doses for the 50, 250, and 1,000 ppm groups over the entire treatment period were 4.25, 17.5, and 69.07 mg/kg/day, respectively, for the F0 males; 6.68, 28.28, and 98.37 mg/kg/day, respectively, for the

F0 females; 4.53, 21.95, and 71.08 mg/kg/day, respectively for the F1 parental males; and 6.72, 29.57, and 99.56 mg/kg/day, respectively, for the F1 parental females. There were no significant treatment-related effects on fertility.

Results from studies in which pregnant rats or rabbits were administered glutaraldehyde orally are presented in Section 3.2.2.6 (Developmental Effects).

3.2.2.6 Developmental Effects

No data were located regarding developmental effects in humans following oral exposure to glutaraldehyde.

Developmental end points have been assessed in rats and rabbits following oral exposure of maternal animals during gestation. Study reports available to ATSDR through the Toxic Substances Control Act (TSCAT) include a developmental toxicity study of rats administered glutaraldehyde in the drinking water during GDs 6–15 (BASF Corp. 1991b) with summary data from range-finding studies that employed oral exposure via the drinking water and via gavage administration, and a developmental toxicity study of rabbits administered glutaraldehyde via gavage during GDs 7–19 (BASF Corp. 1991a) with summary data from range-finding studies that employed oral exposure via the drinking water and via gavage administration. TSCAT submissions (BASF1990l, 1990m, 1991c) contained summary tables for the range-finding studies. There was no evidence of glutaraldehyde-induced effects on numbers of corpora lutea, implantation sites, dead implantations, early and late resorptions, or live or dead fetuses; or gross fetal anomalies among rats administered glutaraldehyde by gavage at doses as high as 50–68 mg/kg/day during GDs 6–15 (BASF Corp. 1991b, 1991c; Ema et al. 1992), rats exposed via the drinking water at doses as high as 51 mg/kg/day during GDs 6–16 (BASF Corp. 1990l, 1991b), rabbits administered gavage doses as high as 25 mg/kg/day during GDs 7–19 (BASF Corp. 1990m, 1991a), or rabbits exposed via the drinking water at doses as high as 23 mg/kg/day during GDs 7–20 (BASF Corp. 1991a, 1991c). Gavage treatment of pregnant rabbits at 22.5 mg/kg/day) resulted in decreased gravid uterine weight (93% less than controls); decreases in numbers of does with fetuses (1/15 versus 15/15 in controls), does with 100% resorptions (9/15 versus 0/15 in controls), postimplantation loss (94% versus 14% in controls); and markedly reduced mean placental and fetal body weights (BASF Corp. 1991a). However, the 22.5 mg/kg/day dose level was maternally toxic, resulting in death (5/15 does) and actual body weight loss among survivors. Significantly lower mean live fetal body weights (6–9% less than controls) were noted at a gavage dose level of 100 mg/kg/day, a dose that resulted in the death of

5/26 pregnant rats; although the next lower dose level (25 mg/kg/day) resulted in 2/21 maternal deaths, there was no significant effect on fetal body weights (Ema et al. 1992).

In a 2-generation oral study, groups of F0 rats were exposed to glutaraldehyde in the drinking water at concentrations resulting in average glutaraldehyde doses of 0, 4.25, 17.5, or 69.07 mg/kg/day for the males and 0, 6.68, 28.28, or 98.37 mg/kg/day for the females; doses to similarly-treated F1 parental rats were 0, 4.53, 21.95, or 71.08 mg/kg/day for the males and 0, 6.72, 29.57, and 99.56 mg/kg/day for the females (Neeper-Bradley and Ballantyne 2000). Significantly depressed mean pup body weight per litter was noted for high-dose F1 pups at postpartum days 21 and 28 (5–11% lower than controls); mean pup body weight gain per litter was 14–19% less than that of controls during lactation days 14–28. Significantly depressed mean pup body weight per litter was noted for high-dose F2 pups at postpartum days 21 and 28 (7–13% lower than controls); for lactation days 14–21 and 21–28, mean pup body weight gain per litter was 17–27% less than that of controls. The effects on pup body weight were likely due to aversion to glutaraldehyde-treated drinking water during and subsequent to weaning (significantly decreased water consumption was observed among both F0 and F1 high-dose parental rats). There were no treatment-related effects on other developmental indices.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-7 and plotted in Figure 3-3.

3.2.2.7 Cancer

No data were located regarding cancer in humans following oral exposure to glutaraldehyde.

Groups of Fischer 344 rats (100/sex/group) were administered glutaraldehyde in the drinking water for up to 2 years at concentrations of 50, 250, or 1,000 ppm (calculated doses in the range of 4–64 mg/kg/day for the males and 6–86 mg/kg/day for the females) (van Miller et al. 2002). Interim sacrifices at 52 and 78 weeks revealed no evidence of treatment-related increased incidences of neoplastic lesions compared to untreated controls. At 104-week terminal sacrifice, significantly increased incidences of LGLL were noted in the spleen and liver of 50, 250, and 1,000 ppm groups of female rats (spleen: 21/47, 22/52, 33/56, respectively, compared to 13/62 controls; liver: 20/47, 22/52, and 37/56, respectively, compared to 12/62 controls). Incidences of LGLL in the glutaraldehyde-treated male rats were not significantly different from that of controls, with the exception of increased LGLL in the liver (but not the spleen) of the 50 ppm group of males at week 104 sacrifice (incidence of 32/52 versus 22/56 for controls). 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 among the glutaraldehyde-treated female rats might possibly have been a result of an abnormally low incidence of LGLL in the control females. Upon evaluation of the study results by a Cancer Assessment Review Committee for the U.S. EPA (EPA 2006), it was determined that the incidences of LGLL were either all within the historical range of three studies from the testing laboratory (19–35%) or the NTP historical control database (14–52%). The Committee did not consider the statistically increased incidences of LGLL in the female F344 rats to be treatment related for the following reasons: (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 (van Miller et al. 2002), in male or female F344 rats or B6C3F1 mice exposed to glutaraldehyde vapor by inhalation for 2 years (NTP 1999), or Wistar rats exposed via the drinking water for 2 years (Confidential 2002). As noted earlier, high incidences of bone marrow hyperplasia and renal tubular pigmentation observed in rats that died prior to terminal sacrifice as well as those surviving to terminal sacrifice were most likely related to low grade hemolytic anemia that accompanied LGLL in these rats (Stromberg et al. 1983; van Miller et al. 2002).

As noted in Section 3.2.1.7 (Cancer), glutaraldehyde is not included in the list of agents evaluated for carcinogenicity by IARC (IARC 2013).

3.2.3 Dermal Exposure

3.2.3.1 Death

No information was located regarding death in humans following dermal exposure to glutaraldehyde.

Available acute lethality studies in which rabbits received dermal application of aqueous glutaraldehyde for 24 hours reported dermal LD_{50} values generally within a range of 898–3,405 mg/kg (Ballantyne 1995; Ballantyne and Jordan 2001; Union Carbide Chem & Plas Co. 1991k, 1991q; Union Carbide Corp. 1992b, 1992c). Aqueous glutaraldehyde concentrations in the range of 45–50% were considered moderately toxic following acute dermal application; 25% glutaraldehyde was considered significantly less toxic, and concentrations ≤10% were not considered to pose a significant acute dermal toxicity hazard (Ballantyne 1995; Ballantyne and Jordan 2001). However, LD_{50} values of 282 mg/kg (Union Carbide Corp. 1992a) and 9,322 mg/kg (BASF Corp. 1990i) were determined in two other studies that

employed 45–50% aqueous glutaraldehyde solutions. In a repeated-dose dermal study of mice (5/dose) administered glutaraldehyde via unoccluded dermal application at glutaraldehyde doses in the range of 0.86–1,024 mg/kg/day (5 days/week for up to 10 applications in a 12-day period), doses ≥510 mg/kg/day resulted in 100% mortality (Union Carbide Chem & Plas Co. 1991y). Deaths occurred after 4–9 applications. Only one death occurred among mice treated at <510 mg/kg/day; the death occurred in a group treated at 41 mg/kg/day and was not considered treatment related.

All reliable LOAEL and LD_{50} values for death in each species and duration category are recorded in Table 3-8.

3.2.3.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each species, duration, and end point for systemic effects are recorded in Table 3-8.

No information was located regarding the following effects in humans or laboratory animals exposed to glutaraldehyde by the dermal route: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and endocrine effects.

Dermal Effects. Glutaraldehyde is widely recognized as a severe dermal irritant. Numerous reports are available in which irritant effects have been associated with dermal exposure to glutaraldehyde; these results were largely obtained for individuals in a variety of occupational settings where glutaraldehyde is used as a germicide (e.g., Bardazzi et al. 1986; Cusano and Luciano 1993; di Prima et al. 1988; Fowler 1989; Hamann et al. 2003; Hansen 1983a, 1983b; Jordan et al. 1972; Kanerva et al. 2000; Kiec-Swierczynska and Krecisz 2001; Kiec-Swierczynska et al. 2001; Kucenic and Belsito 2002; Maibach 1975; Nethercott et al. 1988; Nettis et al. 2002; Ravis et al. 2003; Sanderson and Cronin 1968; Shaffer and Belsito 2000; Stingeni et al. 1995; Tam et al. 1989).

Several human studies were designed to assess glutaraldehyde-induced dermal irritation and sensitization potential at relatively low dermal dose levels. In one study, a total of 109 volunteers received repeated occlusive dermal applications of 0.1, 0.2, and 0.5% aqueous glutaraldehyde to unique sites on the back for a total of 10 induction applications (Union Carbide Corp. 1980). Patches remained in place for 48 hours (72 hours on weekends), followed by removal and readings 15 minutes later for evidence of dermal irritation. A total of 7/109 volunteers exhibited application site erythema and 9 other volunteers exhibited

Table 3-8. Levels of Significant Exposure to Glutaraldehyde – Dermal

Species (strain) number/group	Exposure parameters	Parameters monitored	System	NOAEL	Less serious LOAEL	Serious LOAEL	Results	Reference/comments
ACUTE EXPOSURE								
Death								
Rabbit (albino) 4 M	Once (24 hr occluded) 452, 904, 1,808, 3,616 mg/kg	BW CS GN LE				1,435 mg/kg	LD_{50}=2.54 mL/kg for 50% aqueous glutaraldehyde	Union Carbide Corp. 1992b Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
Rabbit (albino) 4 M	Once (24 hr occluded) 282, 565, 1,130, 2,260 mg/kg	BW CS GN LE				898 mg/kg	LD_{50}=1.59 mL/kg for 50% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991k Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
Rabbit (New Zealand) 5 M, 5 F	Once (24 hr occluded) 2,825, 5,650, 11,300 mg/kg	BW CS GN LE				9,322 mg/kg	LD_{50}=16.5 mL/kg (combined sexes) for 50% aqueous glutaraldehyde	BASF Corp. 1990i Reported doses in mg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
Rabbit (New Zealand) 2 or 5 M, 5 F	Once (24 hr occluded) M: 504, 1,008, 2,016, 4,032, 8,064 mg/kg F: 504, 1,008, 1,411, 2,016 mg/kg	BW CS GN LE				1,008 mg/kg M 1,366 mg/kg F	LD_{50}=2.00 mL/kg (males), 2.71 mL/kg (females) for 45% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991q Reported doses in mg test substance (45% aqueous glutaraldehyde/kg converted to mg glutaraldehyde/kg using specific gravity of 1.12 g/mL
Rabbit (New Zealand) 4 M	Once (24 hr occluded) 126, 252, 504 mg/kg	BW CS GN LE				282 mg/kg	LD_{50}=0.56 mL/kg for 45% aqueous glutaraldehyde	Union Carbide Corp. 1992a Reported doses in mL/kg test substance (45% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.12 g/mL
Rabbit (albino) 4 M	Once (24 hr occluded) 532, 1,065, 2,130, 4,260 mg/kg	BW CS GN LE				2,128 mg/kg	LD_{50}=8.00 mL/kg for 25% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991k Reported doses in mL/kg test substance (25% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.064 g/mL
Rabbit (New Zealand) 2 or 4 M	Once (24 hr occluded) 213, 852, 1,704, 3,408 mg/kg	BW CS GN LE				3,405 mg/kg	LD_{50}=12.8 mL/kg for 25% aqueous glutaraldehyde	Union Carbide Corp. 1992c Reported doses in mL/kg test substance (25% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.064 g/mL

Table 3-8. Levels of Significant Exposure to Glutaraldehyde – Dermal

Species (strain) number/group	Exposure parameters	Parameters monitored	System	NOAEL	Less serious LOAEL	Serious LOAEL	Results	Reference/comments
Mouse (C3H/HeJ) 5 M	12 d, 5 d/wk, 1 x/d (unoccluded) 0.86, 3.9, 7.9, 41, 95, 510, 1,024 mg/kg/d	BW CS GN LE				510 mg/kg	0.086–95 mg/kg/d: no treatment-related deaths 510 and 1,024 mg/kg/d: all mice died	Union Carbide Chem & Plas Co. 1991y Mice received 0.05 mL of various dilutions of 50% aqueous glutaraldehyde; doses estimated using dosing volume and reported mean body weight for each dilution and accounting for proportion of glutaraldehyde for each dilution
Systemic								
Human 41 F (18-35 yr)	Multiple 25-sec exposures to glutaraldehyde vapor at 0.229–0.772 ppm	CS	Ocular		0.39 ppm		Threshold of ocular detection	Cain et al. 2007
Rat (various strains)	4–6-hr exposures to glutaraldehyde vapor	CS	Ocular		3–78 ppm		Clinical signs of ocular irritation	Hoechst Celanese 1981; Union Carbide Chem & Plas Co. 1991p, 1991x Results for multiple studies
Rat (F344) 10 M, 10 F	6 hr/d for 9 exposures in 11 d at vapor concentrations of 0.2–2.09 ppm	CS	Ocular		0.2 ppm		Clinical signs of ocular irritation at 0.2 ppm; dull cornea at 2.09 ppm	Union Carbide Corp. 1992e
Rabbit	Single 24-hr dermal application (unoccluded)	CS	Dermal		0.01–0.05 mL		Signs of moderate dermal irritation at application site following application of 25–50% aqueous glutaraldedyde	Union Carbide Corp. 1992a, 1992b, 1992c Results for multiple studies
Rabbit	Single 1–4 hr dermal application (occluded)	CS	Dermal		0.5 mL		Dose-related persistent primary skin irritation following application of 5–50% aqueous glutaraldehyde	Union Carbide Chem & Plas Co. 1991bb, 1991m; Union Carbide Corp. 1992h, 1992j Results for multiple studies
Rabbit (New Zealand) 2 or 4 M	Once (24 hr occluded) 213, 852, 1,704, 3,408 mg/kg	BW CS GN LE	Dermal		213 mg/kg		Edema and necrosis persisting for 14 d posttreatment	Union Carbide Corp. 1992c Reported doses in mL/kg test substance (25% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.064 g/mL
Rabbit (albino) 4 M	Once (24 hr occluded) 452, 904, 1,808, 3,616 mg/kg	BW CS GN LE	Dermal		452 mg/kg		Edema and necrosis persisting for 14 d posttreatment	Union Carbide Corp. 1992b Reported doses in mL/kg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL

Table 3-8. Levels of Significant Exposure to Glutaraldehyde – Dermal

Species (strain) number/group	Exposure parameters	Parameters monitored	System	NOAEL	Less serious LOAEL	Serious LOAEL	Results	Reference/comments
Rabbit (New Zealand) 5 M, 5 F	Once (24 hr occluded) 900 mg/kg	BW CS GN LE	Dermal		900 mg/kg		Application-site erythema, edema, ecchymosis, necrosis, desquamation, ulceration	Union Carbide Chem & Plas Co. 1991aa Reported doses in mg test substance (2000 mg 45% aqueous glutaraldehyde/kg) converted to mg glutaraldehyde/kg
Rabbit (New Zealand) 5 M, 5 F	Once (24 hr occluded) 2,825, 5,650, 11,300 mg/kg	BW CS GN LE	Dermal		2,825 mg/kg		Application-site eschar formation in all rabbits at all dose levels	BASF Corp. 1990i Reported doses in mg test substance (50% aqueous glutaraldehyde) converted to mg glutaraldehyde/kg using specific gravity of 1.13 g/mL
Rabbit (New Zealand) 6 (sex NS)	Single 24-hr dermal application (occluded)	CS	Dermal		0.5 mL		Eschar formation in 5/6 rabbits within 24 hr following application of 50% aqueous glutaraldehyde; persistent irritation for 14 d posttreatment	BASF Corp. 1990f
Rabbit (New Zealand) 6 (sex NS)	Single 24-hr dermal application (occluded)	CS	Dermal		0.5 mL		Eschar formation in 6/6 rabbits within 24 hr following application of 25% aqueous glutaraldehyde; persistent irritation for 14 d posttreatment	BASF Corp. 1990g
Mouse (C3H/HeJ) 5 M	12 d, 5 d/wk, 1 x/d (unoccluded) 0, 0.86, 3.9, 7.9, 41, 95, 510, 1,024 mg/kg/d	BW CS GN LE	Dermal BW	7.9 mg/kg/d 41 mg/kg/d	41 mg/kg/d	95 mg/kg/d	0.86–41 mg/kg/d: no dermal effects; no body weight effects 95 mg/kg/d: flaky skin at application site; 3% body weight loss 510 mg/kg/d: stained and firm skin at application site; 5/5 died 1,024 mg/kg/d: stained and firm skin, subcutaneous edema at application site; 5/5 died	Union Carbide Chem & Plas Co. 1991y Mice received 0.05 mL of various dilutions of 50% aqueous glutaraldehyde; doses estimated using dosing volume and reported mean body weight for each dilution and accounting for proportion of glutaraldehyde for each dilution

BW = body weight; CS = clinical signs; d = day(s); F = female(s); GN = gross necropsy; hr = hour(s); LD_{50} = lethal dose, 50% kill; LE = lethality; M = male(s); NS = not specified; sec = second(s); wk = week(s); x = time(s); yr = years of age

questionable responses. In another study (Union Carbide Corp. 1966), a group of 21 volunteers were to receive repeated 24-hour occluded dermal applications of 5% aqueous glutaraldehyde; dermal irritation was noted in 15 of the volunteers after two applications; subsequent applications of 1, 2, or 5% aqueous glutaraldehyde under unoccluded conditions resulted in no signs of dermal irritation. The study authors suggested that the irritative effects observed following the initial two applications were attributable to the occlusive material rather than glutaraldehyde. However, the study lacked a group receiving occlusion treatment in the absence of glutaraldehyde and the lack of dermal effects following unoccluded application may have been related to evaporation from the application site. Another group of 40 subjects received repeated dermal applications of 1–5% aqueous glutaraldehyde for periods of 1 or 5 days under occluded or unoccluded conditions for a total of five applications (Union Carbide Corp. 1966). Dermal irritation was observed in all 40 subjects following 5-day occluded application of 5% glutaraldehyde and in 7/40 subjects following 5-day application of 2% aqueous glutaraldehyde, but there was no evidence of dermal irritation following 1-day unoccluded dermal application at 5% aqueous glutaraldehyde.

Numerous reports are available regarding glutaraldehyde-induced contact irritation following dermal application to laboratory animals. For example, as little as 0.01–0.05 mL of 25–50% aqueous glutaraldehyde applied to the skin of rabbits for 24 hours resulted in signs of moderate dermal irritation at the application site (Union Carbide Corp. 1992a, 1992b, 1992c). A single 24-hour occluded dermal application of 0.5 mL of 25 or 50% aqueous glutaraldehyde to the skin of rabbits resulted in signs of severe primary dermal irritation with rapid eschar formation persisting throughout 14 days of posttreatment observation (BASF Corp. 1990f, 1990g). Single occluded dermal application of 0.5 mL of 5–50% aqueous glutaraldehyde to rabbit skin for as little as 1–4 hours resulted in dose-related persistent primary skin irritation (Union Carbide Chem & Plas Co. 1991m; Union Carbide Corp. 1992h, 1992j). In acute lethality studies that employed single 24-hour dermal application to rabbits followed by up to 14 days of posttreatment observation, severe primary dermal irritation (as evidenced by necrosis and rapid eschar formation) was observed at 213 mg glutaraldehyde/kg (Union Carbide Corp. 1992c), 452 mg/kg (Union Carbide Corp. 1992b), and 2,825 mg/kg (BASF Corp. 1990i), the lowest dose level tested in each study. Application site dermal irritation was noted in mice receiving repeated 24-hour dermal applications of glutaraldehyde at doses ≥41 mg glutaraldehyde/kg/day for a total of 10 applications in a 12-day period (Union Carbide Chem & Plas Co. 1991y). Werley et al. (1996) reported signs of application site dermal irritation (mainly minimal erythema and edema) among rats receiving repeated dermal applications of aqueous glutaraldehyde for 4 weeks at doses of 50–150 mg/kg/day; the irritative effects resolved during a 4-week recovery period.

Ocular Effects. Occupational exposure to glutaraldehyde has been commonly associated with ocular irritation (Calder et al. 1992; Jachuck et al. 1989; NIOSH 1987a, 1987b; Pisaniello et al. 1997; Vyas et al. 2000; Waldron 1992; Waters et al. 2003). In some occupational reports that included measurements of personal and/or workplace airborne glutaraldehyde levels, ocular irritation was self-reported at short-term exposure levels as low as 0.05–0.2 ppm). However, these reports do not provide adequate exposure-response data for useful quantitative risk analysis. Severe ocular effects were reported in cases of 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 (Dailey et al. 1993; Unal et al. 2006). Cain et al. (2007) reported a threshold of ocular detection of 0.39 ppm, based on self-reported results from multiple 25-second exposures of 41 nonsmoking female volunteers (18–35 years of age) to glutaraldehyde vapor at 0.229–0.772 ppm.

Numerous reports are available regarding glutaraldehyde-induced effects following ocular instillation of glutaraldehyde to animals. For example, installation of as little as 0.005 mL of a 25–50% aqueous glutaraldehyde solution into rabbit eyes caused severe ocular injury such as necrosis, severe corneal injury, iritis, and swollen and necrosed eyelids (Union Carbide Corp. 1992a, 1992b, 1992c). Traces of corneal injury also occurred following instillation of 0.5 mL of 1% aqueous glutaraldehyde (Union Carbide Corp. 1992a, 1992b). Slight eyelid redness, conjunctival injection, and white discharge were observed in the treated eye of three of six rabbits following 0.1 mL ocular installation of 0.2% aqueous glutaraldehyde; slightly more persistent effects were noted in eyes treated with 0.5% aqueous glutaraldehyde (Union Carbide Chem & Plas Co. 1991k). Another study reported severe corneal injury that persisted for 21 days postinstillation of 0.1 mL of 45% aqueous glutaraldehyde into rabbit eyes (Union Carbide Chem & Plas Co. 1991cc).

Single 4–6-hour exposure of rats to glutaraldehyde vapor at concentrations in the range of 3–78 ppm resulted in clinical signs of ocular irritation (Hoechst Celanese Corp. 1981; Union Carbide Chem & Plas Co. 1991p, 1991x). In one study of repeated exposure to airborne glutaraldehyde, clinical signs of ocular irritation were observed at 0.2 ppm and dull corneas were noted at 2.09 ppm (Union Carbide Corp. 1992e). These effects were the result of direct ocular contact with glutaraldehyde vapor.

Body Weight Effects. No information was located regarding body weight effects in humans following dermal exposure to glutaraldehyde.

Significantly depressed mean body weight gain (20% less than that of controls) was reported in male mice administered a 50% aqueous glutaraldehyde solution dermally via 24-hour occluded patch, 5 days/week for a total of 10 applications in a 12-day period at a dose level of 95 mg/kg/day (Union Carbide Chem & Plas Co. 1991y); there were no significant effects on body weight at doses ≤41 mg/kg/day.

3.2.3.3 Immunological and Lymphoreticular Effects

Numerous reports are available in which dermal patch testing of glutaraldehyde elicited positive results; these results were obtained for individuals in a variety of occupational settings where glutaraldehyde is used as a germicide (e.g., Bardazzi et al. 1986; Cusano and Luciano 1993; di Prima et al. 1988; Fowler 1989; Hamann et al. 2003; Hansen 1983a, 1983b; Jordan et al. 1972; Kanerva et al. 2000; Kiec-Swierczynska and Krecisz 2001; Kiec-Swierczynska et al. 2001; Kucenic and Belsito 2002; Maibach 1975; Nethercott et al. 1988; Nettis et al. 2002; Ravis et al. 2003; Sanderson and Cronin 1968; Shaffer and Belsito 2000; Stingeni et al. 1995; Tam et al. 1989).

Controlled human studies were designed to assess the dermal sensitization potential of glutaraldehyde (Table 3-9). In one study of 109 volunteers that employed repeated occlusive dermal applications of 0.1, 0.2, and 0.5% aqueous glutaraldehyde to unique sites on the back during induction and a single challenge application, no sensitization responses were elicited by challenge at 0.1 or 0.2% glutaraldehyde; challenge at 0.5% glutaraldehyde resulted in one case of erythema and edema and one other case of a questionable reaction (Union Carbide Corp. 1980). In another study (Union Carbide Corp. 1966), a group of 21 volunteers received repeated dermal applications of 5% aqueous glutaraldehyde during induction, followed by challenge application. Based on the severity of reactions provoked by occluded patches during the first two applications, the remaining applications were unoccluded. There were no signs of dermal irritation at any unoccluded site during induction or challenge. Another group of 40 subjects received repeated dermal applications of 1–5% aqueous glutaraldehyde for periods of 1 or 5 days under occluded or unoccluded conditions (Union Carbide Corp. 1966). Dermal irritation was observed in all subjects following 5-day occluded application of 5% glutaraldehyde and in 7/40 subjects following 5-day occluded application of 2% aqueous glutaraldehyde, but there was no evidence of dermal irritation following 1-day unoccluded dermal application at 5% aqueous glutaraldehyde, 5-day occluded application of 1% aqueous glutaraldehyde, or in response to challenge application (2% occluded or 5% unoccluded).

Table 3-9. Summarized Results from Studies Designed to Evaluate Glutaraldehyde-Induced Dermal Hypersensitivity

Reference/study type and subjects	Study design	Results
Union Carbide Corp. 1980 Controlled human study of dermal sensitization potential; 109 volunteers (≥12 years of age)	Induction: ten 48- or 72-hour occlusive dermal applications of 0.1, 0.2, and 0.5% aqueous glutaraldehyde to unique sites on the back (one site per concentration of test material; evaluations for dermal irritation 15 minutes following removal Challenge: single 48-hour application of 0.1, 0.2, and 0.5% aqueous glutaraldehyde to unique sites; evaluations at 15 minutes and 24 hours following removal	0.1% glutaraldehyde: Induction: dermal irritation in 3/109 Challenge: no sensitization 0.2% glutaraldehyde: Induction: dermal irritation in 3/109 Challenge: no sensitization 0.5% glutaraldehyde: Induction: dermal irritation or questionable response in 16/109 Challenge: one case of erythema and edema and one questionable response upon challenge
Union Carbide Corp. 1966 Controlled human study of dermal sensitization potential; 21 ambulatory subjects (age 20 months–55 years)	Induction: 15 24-hour dermal applications of 5% aqueous glutaraldehyde with 24- or 48-hour rest between applications (first 2 applications occluded, remaining applications unoccluded due to severity of irritation during occluded applications) Challenge: single 24-hour application of 5% aqueous glutaraldehyde to unique sites after a 2-week rest period	Induction: during occluded applications, slight to marked erythema in 13/20 (one subject dropped out) Challenge: no sensitization Note: these subjects also received seven occluded dermal applications of 1% glutaraldehyde and three occluded applications of 2% glutaraldehyde in the induction phase, followed by challenge with 2% glutaraldehyde; erythema was noted in one subject after the 7th application of 1% glutaraldehyde; slight erythema was noted in 6/20 subjects following challenge at 2% glutaraldehyde

Table 3-9. Summarized Results from Studies Designed to Evaluate Glutaraldehyde-Induced Dermal Hypersensitivity

Reference/study type and subjects	Study design	Results
Union Carbide Corp. 1966 Controlled human study of dermal sensitization potential; 40 nursing home patients (≥30 years of age)	Induction: one 24-hour occluded dermal application of 5% glutaraldehyde (assumed to be an aqueous solution) immediately followed by a 5-day occluded dermal application of 5% glutaraldehyde, 48-hour rest, 24-hour occluded application of 1% glutaraldehyde to new site, 24-hour rest, 24-hour rest, 24-hour unoccluded application of 5% glutaraldehyde to new site, 48-hour rest, 5-day occluded application of 2% glutaraldehyde to new site, 2-week rest Challenge: 24-hour applications of 2% (occluded) and 5% (unoccluded) glutaraldehyde to new sites	Induction: all subjects exhibited marked erythema from the 5-day occluded application of 5% glutaraldehyde; 6/40 subjects exhibited marked erythema from the 5-day occluded application of 2% glutaraldehyde Challenge: no sensitization
Stern et al. 1989 Dermal contact hypersensitivity study in female guinea pigs (6/group)	Induction: dermal application of 0.3, 1, or 3% glutaraldehyde to the shaved left side of back on each of 14 consecutive days, followed by 7 days of rest Challenge: Dermal application of 10% glutaraldehyde to a new site on left side of back, visual evaluation at 24 and 48 hours postchallenge application, radioassay of tissue biopsies from left and right lumbar regions taken at 48 hours postchallenge Study included vehicle (olive oil:acetone 1:4) and positive control groups	Results of visual inspection: contact hypersensitivity response at 24 and 48 hours postchallenge in the group receiving 3% glutaraldehyde during induction Results of radioassay: contact hypersensitivity response in the lumbar tissue (but not ear tissue) in the group receiving 3% glutaraldehyde during induction Note: Radioassay method more sensitive indicator of hypersensitivity than visual inspection of challenge site

Table 3-9. Summarized Results from Studies Designed to Evaluate Glutaraldehyde-Induced Dermal Hypersensitivity

Reference/study type and subjects	Study design	Results
Stern et al. 1989 Dermal contact hypersensitivity study in female guinea pigs (6/group)	Induction: dermal application of 3% glutaraldehyde to the shaved left side of back on each of 14 consecutive days, followed by 14 days of rest Challenge: dermal application of 10% glutaraldehyde to the shaved left side of back and left ear, visual evaluation at 24 and 48 hours postchallenge application, radioassay of tissue biopsies from left and right lumbar regions and left and right ear taken at 48 hours postchallenge Study included vehicle (olive oil:acetone 1:4) and positive control groups	Results of visual inspection: glutaraldehyde induced contact hypersensitivity response at 24 and 48 hours postchallenge Results of radioassay: contact hypersensitivity response in the lumbar tissue (but not ear tissue)
Stern et al. 1989 Dermal contact hypersensitivity study in female mice (8/group)	Induction: dermal application of 0.3, 1, or 3% glutaraldehyde to the ventral side on each of 5 or 14 consecutive days, followed by 4 days of rest Challenge: dermal application of 10% glutaraldehyde to the left ear, radioassay of biopsied ear collected 24 hours postchallenge Study included negative, vehicle (olive oil:acetone 1:4), and positive control groups	No evidence of a contact hypersensitivity response
Stern et al. 1989 Dermal contact hypersensitivity study in female mice (8/group)	Induction: dermal application of 0.3, 1, or 3% glutaraldehyde to the upper dorsal side on each of 5 consecutive days, followed by 7 days of rest Challenge: Dermal application of 10% glutaraldehyde to the left ear, radioassay of biopsied ears and dorsal skin collected 48 hours postchallenge Study included negative, vehicle (olive oil:acetone 1:4), and positive control groups	Contact hypersensitivity response at all dose levels of glutaraldehyde administered during induction, more evident in ear tissues than dorsal skin tissues

Table 3-9. Summarized Results from Studies Designed to Evaluate Glutaraldehyde-Induced Dermal Hypersensitivity

Reference/study type and subjects	Study design	Results
Descotes 1988 Mouse ear sensitization assay; 18 female BALB/c mice	Induction: two applications (2 days apart) of 1% glutaraldehyde (in complete Freund's adjuvant) to the ear Challenge: Application of 10% glutaraldehyde to the ear on day 9 and measurement of ear thickness immediately following application and 24 hours later	Significantly increased mean ear thickness
Azadi et al. 2004 Mouse ear swelling test; female BALB/c mice (8/group)	Induction: application of 0.1, 0.75, or 2.5% glutaraldehyde (in dimethyl formamide) to the ear on 3 consecutive days; ear thickness measured prior to challenge Challenge: application of 2.5% glutaraldehyde to the ear; ear thickness measured at 30 minutes and 24 and 48 hours postchallenge application	Significantly increased ear thickness at 30 minutes postchallenge in group administered 2.5% glutaraldehyde during induction; delayed-type hypersensitivity response (at 48 hours postchallenge application) in mice administered 0.1 or 0.75% glutaraldehyde during induction
Azadi et al. 2004 Local lymph node assay; female CBA and BALB/c mice	Application of 0.1, 0.75, or 2.5% glutaraldehyde (in dimethyl formamide) to the ear on 3 consecutive days Study included vehicle and positive controls	Significantly increased lymphocyte proliferation in cervical draining lymph nodes of mice treated with 0.75 or 2.5% glutaraldehyde; significantly increased percentage of B200+ cells at all glutaraldehyde dose levels; significantly increased total serum IgE at highest dose
Hilton et al. 1998 Local lymph node assay; female CBA/ca mice (4/group)	Application of 0.25, 0.5, 1, 2.5, or 5% glutaraldehyde (in acetone or dimethyl formamide) to each ear daily for 3 consecutive days, followed by intravenous injection of ^{3}H-methyl thymidine on day 5 and sacrifice 5 hours later for harvest of draining auricular lymph nodes Study included vehicle controls	Glutaraldehyde induces concentration-related significant increase in lymph node cell proliferative activity at all but the lowest concentration (0.25%)

The potential for glutaraldehyde to induce dermal contact hypersensitivity in laboratory animals has been evaluated in several studies; results are mixed (Table 3-9). Some studies reported evidence of glutaraldehyde-induced contact hypersensitivity (Azadi et al. 2004; Descotes 1988; Hilton et al. 1998; Stern et al. 1989). No evidence of glutaraldehyde-induced contact hypersensitivity was observed in another study (BASF 2013).

Two studies evaluated the potential for glutaraldehyde-induced hypersensitivity following dermal exposure, as indicated by increases in serum IgE. A 4-fold increase in serum IgE was reported for mice receiving dermal application of 25% glutaraldehyde (in acetone), followed 1 week later by 12.5% glutaraldehyde applied to the ear (Ballantyne 1995). In another study designed to assess total IgE antibody production following dermal exposure to glutaraldehyde and other chemicals, female BALB/c mice received two dermal administrations (7 days apart) for total application of 0–9.38 mg glutaraldehyde in acetone:water (50:50) or 18.75 mg aqueous glutaraldehyde on the shaved flank (first application) and dorsal ear (second application) (Potter and Wederbrand 1995). Analysis of serum collected 14 days following the initial dermal application revealed significantly increased total IgE (approximately 4-fold greater than controls) at the total glutaraldehyde dose of 9.38 mg, but no significant increase at the 18.75 mg dose level. The difference in responses may have been related to the inclusion of acetone as a solvent for the 0–9.38 mg dose levels; however, an acetone vehicle control group was not mentioned in the study report.

No studies were located regarding the following effects associated with dermal exposure of humans or animals to glutaraldehyde:

3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Glutaraldehyde has been widely implicated as the cause of colitis and diarrhea following endoscopy or sigmoidoscopy procedures, the likely result of contact irritation (e.g., Ahishali et al. 2009; Birnbaum et al. 1995; Dolce et al. 1995; Durante et al. 1992; Fukunaga and Khatibi 2000; Hanson et al. 1998; Rozen et al. 1994; Shih et al. 2011; Stein et al. 2001; West et al. 1995).

3.3 GENOTOXICITY

The potential genotoxicity of glutaraldehyde has been assessed in a variety of *in vitro* and *in vivo* test systems; available results are summarized in Tables 3-10 and 3-11, respectively.

Glutaraldehyde did not induce mutations in *Salmonella typhimurium* strains TA98, TA1535, TA1537, or TA1538 either with or without exogenous metabolic activation (Haworth et al. 1983; NTP 1993, 1999; Sakagami et al. 1988a, 1988b; Sasaki and Endo 1978; Slesinski et al. 1983; Union Carbide Chem & Plas Co. 1991ii; Vergnes and Ballantyne 2002). Glutaraldehyde was also nonmutagenic in a mixture of *S. typhimurium* strains TA7001, TA7002, TA7003, TA7004, TA7005, and TA7006 (equal proportions) in the absence of exogenous metabolic activation (Kamber et al. 2009). Positive results were obtained in most assays using *S. typhimurium* strains TA102, TA104, TA2638, BA-9, and BA-13 in the absence of exogenous metabolic activation; most of these assays did not include test results in the presence of exogenous metabolic activation (Dillon et al. 1998; Jung et al. 1992; Levin et al. 1982; Marnett et al. 1985; NTP 1993, 1999; Ruiz-Rubio et al. 1985; Watanabe et al. 1998; Wilcox et al. 1990).

Mixed responses were obtained in gene mutation assays using *S. typhimurium* strain TA100. Mutations were not induced in the presence or absence of exogenous metabolic activation in several of these assays (Sakagami et al. 1988a, 1988b; Sasaki and Endo 1978; Slesinski et al. 1983). A weakly positive result was obtained in the presence (but not the absence) of exogenous metabolic activation in one study (Vergnes and Ballantyne 2002). Results varied among performing laboratories as well. In similarly designed assays both in the presence and absence of exogenous metabolic activation, negative results were obtained in one laboratory, weakly positive results in another laboratory, and clearly positive results in a third laboratory (results from one or more of these laboratories available in Dillon et al. 1998; Haworth et al. 1983; and NTP 1993, 1999).

Gene mutation assays using *Escherichia coli* provided mixed results as well; the assays were performed in the absence of exogenous metabolic activation. Glutaraldehyde induced mutations in *E. coli* strain WP2 *uvrA* (pKM101), but not strain WP2 (pKM101) in one set of assays (Wilcox et al. 1990), but induced mutations in both strains in another set of assays (Watanabe et al. 1998). Glutaraldehyde did not induce mutations in *E. coli* strain WP2 *uvrA* in yet another assay (Hemminki et al. 1980).

Glutaraldehyde induced gene mutations in human TK6 lymphoblasts (St. Clair et al. 1991) and in the mouse lymphoma cell line (L5178Y) (McGregor et al. 1988) in the absence of exogenous metabolic

Table 3-10. Genotoxicity of Glutaraldehyde *In Vitro*

Species/test system	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium TA100	Gene mutation	–	–	Slesinski et al. 1983
S. typhimurium TA100	Gene mutation	–	–	Sasaki and Endo 1978
S. typhimurium TA100	Gene mutation	–[a]	–[a]	Haworth et al. 1983; NTP 1993, 1999
S. typhimurium TA100	Gene mutation	(+)[b]	(+)[b]	Haworth et al. 1983; NTP 1993, 1999
S. typhimurium TA100	Gene mutation	+[c]	+[c]	Dillon et al. 1998; NTP 1993, 1999
S. typhimurium TA100	Gene mutation	(+)	–	Vergnes and Ballantyne 2002
S. typhimurium TA100	Gene mutation	–	–	Sakagami et al. 1988a, 1988b
S. typhimurium TA98	Gene mutation	–[a,b]	–[a,b]	Haworth et al. 1983; NTP 1993, 1999
S. typhimurium TA98	Gene mutation	–	–	Sakagami et al. 1988b
S. typhimurium TA98	Gene mutation	–	–	Sasaki and Endo 1978
S. typhimurium TA98	Gene mutation	–	–	Slesinski et al. 1983
S. typhimurium TA98	Gene mutation	–	–	Union Carbide Chem & Plas Co. 1991ii
S. typhimurium TA98	Gene mutation	–	–	Vergnes and Ballantyne 2002
S. typhimurium TA1535, TA1537, TA1538	Gene mutation	–	–	Slesinski et al. 1983
S. typhimurium TA1535, TA1537, TA1538	Gene mutation	–	–	Union Carbide Chem & Plas Co. 1991ii
S. typhimurium TA1535, TA1537, TA1538	Gene mutation	–	–	Vergnes and Ballantyne 2002
S. typhimurium TA1535, TA1537	Gene mutation	–[a,b]	–[a,b]	Haworth et al. 1983; NTP 1993, 1999
S. typhimurium TA102	Gene mutation	No data	+	Wilcox et al. 1990
S. typhimurium TA102	Gene mutation	No data	+[d]	Jung et al. 1992
S. typhimurium TA102	Gene mutation	No data	–	Levin et al. 1982
S. *typhimurium* TA102, TA104	Gene mutation	(+)[c]	(+)[c]	Dillon et al. 1998; NTP 1993, 1999
S. typhimurium TA102, TA104	Gene mutation	No data	+	Marnett et al. 1985

Table 3-10. Genotoxicity of Glutaraldehyde *In Vitro*

Species/test system	End point	Results		Reference
		With activation	Without activation	
S. typhimurium TA2638	Gene mutation	No data	+	Levin et al. 1982
S. typhimurium TA102, TA2638	Gene mutation	–	+	Watanabe et al. 1998
S. typhimurium BA-9	Gene mutation	No data	+	Ruiz-Rubio et al. 1985
S. typhimurium TA7001, TA7002, TA7003, TA7004, TA7005, TA7006 (mixture of equal proportions)	Gene mutation	No data	–	Kamber et al. 2009
S. typhimurium BA-13	Gene mutation	No data	+	Ruiz-Rubio et al. 1985
Escherichia coli WP2 (pKM101)	Gene mutation	No data	–	Wilcox et al. 1990
E. coli WP2 *uvrA* (pKM101)	Gene mutation	No data	+	Wilcox et al. 1990
E. coli WP2 (pKM101); WP2 *uvrA* (pKM101)	Gene mutation	No data	+	Watanabe et al. 1998
E. coli WP2 *uvrA*	Gene mutation	No data	–	Hemminki et al. 1980
S. typhimurium TA1535/pSK1002	DNA damage/repair (*umu* test)	+	+	Sakagami et al. 1988a
E. coli WP2 *uvrA* ZA12	DNA damage/repair	No data	+	Nunoshiba et al. 1991
E. coli WP2 *uvrA* CM561	DNA damage/repair	No data	+	Nunoshiba et al. 1991
E. coli PQ37	DNA damage/repair (SOS chromotest)	–	–	Von der Hude et al. 1988
Bacillus subtilis M-45 (rec^-), H-17 (rec^+)	DNA damage/repair (liquid *rec* assay)	+	+	Sakagami et al. 1988b
E. coli WP2 *uvrA* ZA60	DNA damage/repair	No data	+	Nunoshiba et al. 1991
Eukaryotic organisms:				
Mammalian cells:				
Human TK6 lymphoblasts	Gene mutation	No data	+	St. Clair et al. 1991
Mouse lymphoma cell line (L5178Y)	Gene mutation	No data	+	McGregor et al. 1988; NTP 1993, 1999
Chinese hamster ovary cells	Gene mutation	–	–	Vergnes and Ballantyne 2002
Chinese hamster ovary cells	Gene mutation	–	–	Slesinski et al. 1983
Chinese hamster ovary cells	Gene mutation	–	–	Union Carbide Chem & Plas Co. 1991gg
Chinese hamster ovary cells	Gene mutation	–	–	Union Carbide Chem & Plas Co. 1991hh

Table 3-10. Genotoxicity of Glutaraldehyde *In Vitro*

Species/test system	End point	Results: With activation	Results: Without activation	Reference
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Union Carbide Chem & Plas Co. 1991jj
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Vergnes and Ballantyne 2002
Chinese hamster ovary cells	Chromosomal aberrations	–	+[e]	Galloway et al. 1985; NTP 1993, 1999
Chinese hamster ovary cells	Chromosomal aberrations	–	–[f]	Galloway et al. 1985; NTP 1993, 1999
Chinese hamster ovary cells	Chromosomal aberrations	(+)[g]	(+)[h]	Tsai et al. 2000
Chinese hamster ovary cells	Sister chromatid exchange	–	–	Slesinski et al. 1983
Chinese hamster ovary cells	Sister chromatid exchange	–	–	Union Carbide Chem & Plas Co. 1991gg
Chinese hamster ovary cells	Sister chromatid exchange	+[i]	+[i]	Galloway et al. 1985; NTP 1993, 1999
Chinese hamster V79 lung fibroblasts	Sister chromatid exchange	No data	+	Speit et al. 2008
Chinese hamster V79 lung fibroblasts	Micronuclei	–	–	Tsai et al. 2000
Chinese hamster ovary cells	Micronuclei	No data	+	Speit et al. 2008
Chinese hamster V79 lung fibroblasts	DNA damage	No data	–	Speit et al. 2008
Human lung epithelial carcinoma cells (A549)	DNA double-strand breaks	No data	+/–	Vock et al. 1999
Rat primary hepatocytes	DNA strand breaks	No data	–	Kuchenmeister et al. 1998
Human TK6 lymphoblasts	DNA-protein cross-links	No data	+	St. Clair et al. 1991
Rat primary hepatocytes	Unscheduled DNA synthesis	No data	+	St. Clair et al. 1991
Rat primary hepatocytes	Unscheduled DNA synthesis	No data	–	Slesinski et al. 1983
Rat primary hepatocytes	Unscheduled DNA synthesis	No data	–	Union Carbide Chem & Plas Co 1991gg
Syrian hamster embryo cells	Unscheduled DNA synthesis	–	–	Zeiger et al. 2005

Table 3-10. Genotoxicity of Glutaraldehyde *In Vitro*

Species/test system	End point	Results: With activation	Results: Without activation	Reference
Syrian hamster embryo cells	Cell transformation	No data	–	Yamaguchi and Tsutsui 2003

[a]Study performed at Case Western Reserve University.
[b]Study performed at EG&G Mason Research Institute.
[c]Study performed at Inveresk Research International.
[d]Positive results at two of three laboratories, a weakly positive result at the other laboratory.
[e]Study performed at Columbia University.
[f]Study performed at Litton Bionetics, Inc.
[g]1.8-fold increase relative to negative control.
[h]1.6-fold increase relative to negative control.
[i]Positive results at two separate laboratories (Columbia University and Litton Bionetics, Inc.).

– = negative result; + = positive result; +/– = inconclusive result; (+) = weakly positive result;
DNA = deoxyribonucleic acid

Table 3-11. Genotoxicity of Glutaraldehyde *In Vivo*

Species/test system	End point	Results	Reference
Rat (bone marrow)	Chromosomal aberrations	–	Confidential 1987a
Rat (bone marrow)	Chromosomal aberrations	–	Vergnes and Ballantyne 2002
Mouse (bone marrow)	Chromosomal aberrations	+[a]	NTP 1999
Mouse (peripheral blood)	Micronucleus formation	–	Vergnes and Ballantyne 2002
Mouse (peripheral blood)	Micronucleus formation	–[b]	NTP 1999
Mouse (bone marrow)	Micronucleus formation	(+)[c]	NTP 1999
Mouse (bone marrow)	Micronucleus formation	–[d]	NTP 1999
Rat (testis)	DNA cross links	–	Confidential 1987b
Rat (testis)	DNA strand breaks	–	Confidential 1987c
Rat (hepatocytes)	Unscheduled DNA synthesis	–	Mirsalis et al. 1989
Mouse (sperm cells)	Dominant lethality	–	NTP 1993, 1999
Drosophila	Sex-linked recessive lethal mutations	–	Yoon et al. 1985; Zimmering et al. 1989

[a]Negative result at 17 hours posttreatment, but positive results at 36 hours posttreatment.
[b]Repeated inhalation exposure of male and female mice for 13 weeks at glutaraldehyde concentrations up to 0.5 ppm.
[c]Single intraperitoneal injection.
[d]Three daily intraperitoneal injections, two trials.

– = negative result; + = positive result; –/+ = equivocal result; (+) = weakly positive result; DNA = deoxyribonucleic acid

activation. Glutaraldehyde did not induce gene mutations in several assays using Chinese hamster ovary cells in both the presence and absence of exogenous metabolic activation (Slesinski et al. 1983; Union Carbide Chem & Plas Co. 1991gg, 1991hh).

Assays designed to evaluate potential for glutaraldehyde to induce DNA damage/repair provided mostly positive results. Positive results were obtained for *S. typhimurium* strain TA1535/pSK1002 in the *umu* test both in the presence and absence of exogenous metabolic activation (Sakagami et al. 1988b), *E. coli* strains WP2 *uvrA* ZA12, WP2 *uvrA* ZA60, and WP2 *uvrA* CM561 in the absence of exogenous metabolic activation (Nunoshiba et al. 1991), and in a liquid *rec* assay using *Bacillus subtilis* strains M-45 (rec^-) and H-17 (rec^+) in both the presence and absence of exogenous metabolic activation (Sakagami et al. 1988a). Glutaraldehyde did not induce DNA damage/repair in an assay using *E. coli* strain PQ37 in the presence of exogenous metabolic activation (von der Hude et al. 1988). Glutaraldehyde did not induce DNA strand breaks in Chinese hamster V79 lung fibroblasts (Speit et al. 2008) or rat primary hepatocytes (Kuchenmeister et al. 1998) in the absence of exogenous metabolic activation. Inconclusive results were obtained for glutaraldehyde-induced DNA double-strand breaks in human lung epithelial carcinoma cells (A549) (Vock et al. 1999).

DNA-protein cross-links were noted in human TK6 lymphoblasts exposed to glutaraldehyde (St. Clair et al. 1991). Glutaraldehyde induced unscheduled DNA synthesis in rat primary hepatocytes in one assay (St. Clair et al. 1991), but not in two other assays (Slesinski et al. 1983; Union Carbide Chem & Plas Co. 1991gg). In Syrian hamster embryo cells, glutaraldehyde did not induce unscheduled DNA synthesis either in the presence or absence of exogenous metabolic activation (Zeiger et al. 2005), or cell transformation in the absence of exogenous metabolic activation (Yamaguchi and Tsutsui 2003).

In assays that assessed the potential for glutaraldehyde to induce chromosomal aberrations in Chinese hamster ovary cells, two assays were negative in both the presence and absence of exogenous metabolic activation (Union Carbide Chem & Plas Co. 1991jj; Vergnes and Ballantyne 2002). In a third study that included assays in two separate laboratories, the results in the absence of exogenous metabolic activation were positive in one laboratory and negative in the other laboratory; both laboratories reported weakly positive results in the presence of exogenous metabolic activation (Galloway et al. 1985). In assays of Chinese hamster ovary cells for glutaraldehyde-induced sister chromatid exchange, negative (Slesinski et al. 1983; Union Carbide Chem & Plas Co. 1991gg) and positive (Galloway et al. 1985) or weakly positive (Tsai et al. 2000) results were obtained both in the presence and absence of exogenous metabolic activation. Glutaraldehyde induced sister chromatid exchange and micronuclei in Chinese hamster V79

lung fibroblasts in the absence of exogenous metabolic activation (Speit et al. 2008), but did not induce micronuclei in Chinese hamster ovary cells in the presence or absence of exogenous metabolic activation (Tsai et al. 2000).

The potential for glutaraldehyde to act as a genotoxic agent has been assessed in a number of *in vivo* assays as well; results are mostly negative. Glutaraldehyde did not induce chromosomal aberrations in bone marrow cells (type not specified) from male and female Sprague-Dawley rats treated by gavage once at 140–200 mg/kg or repeatedly at 20–28 mg/kg/day (Confidential 1987a), or polychromatophils from bone marrow of other male and female Sprague-Dawley rats treated by single gavage at 7.5–60 mg/kg in another study (Vergnes and Ballantyne 2002). Negative results were obtained in one trial of male B6C3F1 mice treated with glutaraldehyde by intraperitoneal injection at 15–60 mg/kg and assessed for chromosomal aberrations in the bone marrow at 17 hours postinjection; positive results were obtained in two other trials at 50 and/or 60 mg/kg with assessment at 36 hours postinjection (NTP 1999).

Glutaraldehyde did not induce micronucleus formation in the peripheral blood of male or female Swiss-Webster mice following gavage administration at 40–125 mg/kg (Vergnes and Ballantyne 2002) or male B6C3F1 mice repeatedly exposed to glutaraldehyde vapor at 0.0625–0.5 ppm for 13 weeks (NTP 1999). A positive result for micronucleus formation was obtained in assessment of bone marrow from male B6C3F1 mice administered single intraperitoneal injection of glutaraldehyde at 15, 50, or 60 mg/kg (but not at 30 mg/kg); however, negative results were obtained in a similar protocol that included 3 daily intraperitoneal injections at 5–20 mg/kg/day (NTP 1999).

Evaluation of DNA from testes of Sprague-Dawley rats administered glutaraldehyde by single gavage at 18–55 mg/kg or five daily doses at 9–28 mg/kg/day revealed no evidence of treatment-related cross links or strand breaks (Confidential 1987b, 1987c). Glutaraldehyde did not induce unscheduled DNA synthesis in hepatocytes from male Fischer-344 rats treated by gavage once at 30–600 mg/kg (Mirsalis et al. 1989), dominant lethality following gavage treatment of male JCL-ICR mice with 30 or 60 mg glutaraldehyde/kg and mating with untreated females for 6 weeks (NTP 1993, 1999), or sex-linked recessive lethal mutations in Drosophila (Yoon et al. 1985; Zimmering et al. 1989).

In summary, the available *in vitro* data suggest that glutaraldehyde is weakly mutagenic in bacteria and mammalian cell lines. Varibility in test protocol among the various mutagenicity assays may be responsible for at least some of the variability in results. There is some evidence for glutaraldehyde-induced chromosomal aberrations, sister chromatid exchange, and micronuclei in mammalian cells

systems. Glutaraldehyde does not appear to cause DNA damage or cell transformation in mammalian cell systems. Mostly negative results were obtained in assays for glutaraldehyde-induced unscheduled DNA synthesis in mammalian cell systems. Available *in vivo* data do not generally provide support for a genotoxic role for glutaraldehyde (five studies reported negative results, one study reported a positive result, and another study reported a weakly positive result); however, data are limited. Glutaraldehyde did not induce DNA cross-links or strand breaks, unscheduled DNA synthesis, or dominant lethality in rats and/or mice, or sex-linked recessive lethal mutations in Drosophila. Negative or equivocal/weakly positive results were reported from assays of glutaraldehyde-induced chromosomal aberrations and micronuclei in mouse bone marrow.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Information regarding absorption via the inhalation route is limited to observations of systemic effects such as toxic hepatitis in mice following inhalation of glutaraldehyde for 24 hours at a reported concentration of 0.133 mg/L (Varpela et al. 1971). No quantitative data were located regarding absorption of inhaled glutaraldehyde.

3.4.1.2 Oral Exposure

No human data were located regarding absorption following oral exposure to glutaraldehyde.

Following gavage administration of radiolabeled glutaraldehyde to male Fischer rats at a mean dose of 68.5 mg/kg (Union Carbide Chem & Plas Co. 1991ff), radioactivity was detected in expired $^{14}CO_2$ and urine, indicating that gastrointestinal absorption of glutaraldehyde and/or its metabolites occurs. No quantitative data were located regarding absorption following oral exposure of animals to glutaraldehyde.

3.4.1.3 Dermal Exposure

In a material balance study, male and female Fischer 344 rats received aqueous ^{14}C-glutaraldehyde to 12–15% of the total body surface under occluded conditions for 24 hours at concentrations resulting in estimated doses of up to 63 mg/kg to males and up to102 mg/kg to females (McKelvey et al. 1992). Based on recovery of radioactivity from skin and dressing, application materials and cage washings,

expired $^{14}CO_2$, urine, feces, and carcass, percutaneous absorption of glutaraldehyde and/or its metabolites was estimated to have been 4–9% of the administered dose. Similar administration of ^{14}C-glutaraldehyde to male and female New Zealand white rabbits resulted in percutaneous absorption of approximately 33–53% of an administered 60 mg/kg dose.

In a pharmacokinetic study performed on rats and rabbits under conditions similar to those employed in the material balance study, calculated dermal absorption rate constants ranged from 0.2 to 2 per hour (McKelvey et al. 1992). Absorption was greater in the rabbits than the rats; estimates of dermal absorption in the pharmacokinetic study were less than those estimated in the material balance study.

A material balance study assessed dermal penetration of ^{14}C-glutaraldehyde through 1-inch disks of skin taken from rats, mice, guinea pigs, rabbits, and humans (women undergoing reconstructive mammoplasty) (Ballantyne 1995; Frantz et al. 1993). At the highest dose level (7.5% glutaraldehyde), estimated dermal penetration of the administered dose was 0.2% for the human skin compared to 0.7% for the animal species (range of 0.05% for the female rat skin to 1.73% for the male mouse skin). Among the laboratory animal species, absorption rates ranged from 0.804 mg/cm^2/hour for the male rat skin to 2.510 mg/cm^2/hour for the female rabbit skin; the absorption rate for the human skin was 1.581 mg/cm^2/hour. The results for the *in vitro* rat skin sample compare to the *in vivo* results from McKelvey et al. (1992) when normalizing for total treated skin surface area (1.77 cm^2 for the *in vitro* rat skin sample compared to 144 cm^2 for the treated area in the *in vivo* study).

Reifenrath et al. (1985) investigated the *in vitro* percutaneous penetration of 10% aqueous glutaraldehyde through isolated human thin stratum corneum (chest and abdomen), abdominal epidermis, and thick stratum corneum (blister tops from soles) during 1 hour postapplication. Penetration of the applied dose measured 2.8–4.4% for the epidermis and 3.3–13.8% for the thin stratum corneum; there was no indication of penetration through the thick stratum corneum.

3.4.1.4 Other Routes of Exposure

Based on the use of glutaraldehyde as a fixative in human root canal preparations, the absorption of glutaraldehyde from canine and incisor pulpotomy sites was assessed in dogs (Myers et al. 1986). Pulpotomy sites received a cotton pellet containing 5.6 µCi of ^{14}C-glutaraldehyde (as a 2.5% aqueous solution) for 5 minutes. Based on measurements of blood, urine, and expired air for 90 minutes following

removal of the pellet and assessment of radioactivity in tissues, it was determined that approximately 3% of the dose had been absorbed from the site.

3.4.2 Distribution

In animal studies involving administration of radiolabeled glutaraldehyde, the proportion of radioactivity in various tissues varied according to route of exposure.

3.4.2.1 Inhalation Exposure

Information regarding distribution following inhalation exposure to glutaraldehyde is limited to the observation of toxic hepatitis in mice following inhalation of glutaraldehyde for 24 hours at a reported concentration of 0.133 mg/L, which indicates that systemic distribution of parent compound and/or its metabolites occurs (Varpela et al. 1971).

3.4.2.2 Oral Exposure

No information was located regarding distribution following oral exposure of humans to glutaraldehyde.

Results of one animal study indicate that glutaraldehyde and/or its metabolites are distributed systemically following oral exposure. At 48 hours following gavage administration of ^{14}C-glutaraldehyde to male Fischer rats at a mean dose of 68.5 mg/kg (Union Carbide Chem & Plas Co. 1991ff), an average of 22% of the administered radioactivity was recovered in the carcass. Mean concentrations or radioactivity were 58 µg glutaraldehyde/g wet tissue in the stomach, 21µg/g in the kidney, 19 µg/g in the esophagus, 8 µg/g in the liver, 7 µg/g in the spleen, and 5 µg/g in the trachea, 5 µg/g in blood cells, and 4 µg/g in lungs. Lesser amounts were detected in bladder, brain, fat, heart, muscle, plasma, and testis.

3.4.2.3 Dermal Exposure

No information was located regarding distribution following dermal exposure of humans to glutaraldehyde.

Male and female Fischer 344 rats and New Zealand white rabbits received dermal application of aqueous ^{14}C-glutaraldehyde under occluded conditions for 24 hours (McKelvey et al. 1992). Of the absorbed radioactivity (4–9 and 33–53% of the administered dose for rats and rabbits, respectively), the highest

concentrations of radioactivity were in found in bladder, bone marrow, and kidney of the male rats; lymph node, trachea, and kidney of the female rats; urinary bladder, kidney, pancreas, spleen, and salivary gland of the male rabbits; and blood cells, kidney, liver, lung, and spleen of the female rabbits. Smaller concentrations were observed in a wide variety of other tissues and organs.

3.4.2.4 Other Routes of Exposure

Male and female Fischer 344 rats and New Zealand white rabbits received aqueous ^{14}C-glutaraldehyde via intravenous injection (McKelvey et al. 1992). At 24 hours postinjection, approximately 3–7 and 4–12% of the administered dose was recovered in tissues of the rats and rabbits, respectively. The highest concentrations of radioactivity were in blood cells and certain well-perfused tissues (spleen, lung, liver, kidney, and bone marrow); lesser concentrations were observed in a wide variety of other tissues and organs.

Groups of rats were infused (intravenously) with 10 µCi of ^{14}C-glutaraldehyde over a 1-minute period and assessed for up to 3 days postinfusion for the distribution of radioactivity between plasma and blood cells (Ranly and Horn 1990). During the postinfusion period, the ratio of red blood cell to plasma radioactivity varied between 2 and 3. The higher content in the cellular fraction was indicative of incorporation into red blood cells. During the 3-day postinfusion period, a 6-fold reduction was observed for radioactivity in the red blood cells and plasma, indicating similarity in elimination rates. Ranly et al. (1990) infused rats (intravenously) with ^{14}C-glutaraldehyde, followed by sacrifice at 5 or 60 minutes postinfusion to assess the cyctolic, membrane, and nuclear fractions of radioactivity in liver cells. Significant radioactivity was associated with cytosol and membrane fractions, but not nuclear fractions.

Canine and incisor pulpotomy sites of dogs received a cotton pellet containing 5.6 µCi of ^{14}C-glutaraldehyde (as a 2.5% aqueous solution) for 5 minutes (Myers et al. 1986). Examination of tissues extracted at sacrifice 90 minutes following the glutaraldehyde treatment revealed that muscle contained approximately 50% of the absorbed dose (3% of the applied dose), with 12% in red blood cells and lesser amounts (in descending order) in plasma, liver, lung, kidney, heart, and spleen. A tissue-to-plasma ratio of 2.21 for red blood cells suggested some degree of binding; tissue-to-plasma ratios for other tissues were lower, indicating little or no binding affinity.

3.4.3 Metabolism

Beauchamp et al. (1992) reviewed available data regarding the pharmacokinetics of glutaraldehyde and other aldehydes. Based on results from *in vivo* studies and *in vitro* assays, Beauchamp et al. (1992) proposed the metabolic pathway for glutaraldehyde shown in Figure 3-4. According to the metabolic scheme, glutaraldehyde undergoes oxidation to form glutaric γ-semialdehyde (step 1), which is oxidized to glutaric acid (step 2). Synthesis of a coenzyme A (CoA) thioester, by a thiokinase reaction or transfer of CoA from succinyl CoA catalyzed by a thiophorase, results in further metabolism to glutaryl CoA (step 3), followed by reduction to glutaconyl CoA by glutaryl CoA dehydrogenase (step 4), production of crotonyl CoA via decarboxylation which results in the release of CO_2 (step 5), hydration to β-hydroxy-butyryl CoA by enoyl CoA hydratase (step 6), conversion to acetyl CoA (step 7), and oxidation to CO_2 (step 8). Results of *in vitro* assays suggest the involvement of NAD^+ and FAD^+ electron transport systems in reduction reactions.

In an *in vitro* assay of ^{14}C-glutaraldehyde-incubated rat liver cells, glutaraldehyde was metabolized to $^{14}CO_2$ (Ranly et al. 1990). However, no significant radioactivity was detected in isolated nucleic acids.

In another *in vitro* assay that assessed the production of $^{14}CO_2$ by ^{14}C-glutaraldehyde-treated rat red blood cells, uptake of radioactivity by red blood cells was approximately 20% of the dose. However, the red blood cells did not appear to metabolize the glutaraldehyde as demonstrated by similarly low amounts of $^{14}CO_2$ among intact and hemolyzed red blood cells (Ranly and Horn 1990). Similar assessment using intact and denatured liver tissue resulted in an 18-fold higher production of $^{14}CO_2$ in the intact liver tissue compared to that of denatured liver tissue and intact and hemolyzed red blood cells.

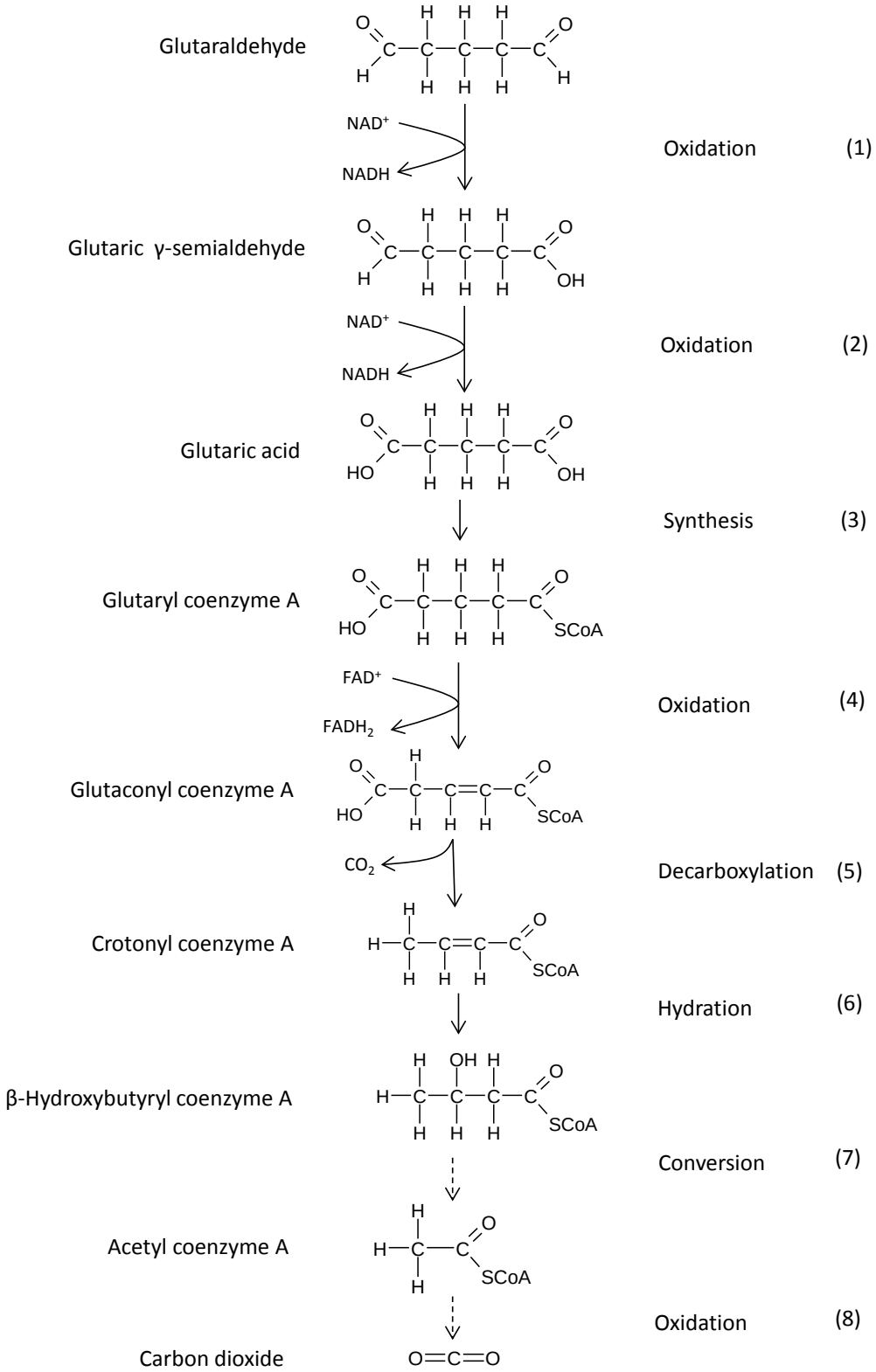
3.4.4 Elimination and Excretion

In animal studies involving administration of radiolabeled glutaraldehyde, the proportion of radioactivity in urine and feces varied according to route of exposure.

3.4.4.1 Inhalation Exposure

No information was located regarding elimination or excretion in humans or animals following inhalation exposure to glutaraldehyde.

Figure 3-4. Proposed Metabolic Scheme for Glutaraldehyde



Source: Beauchamp et al. 1992

3.4.4.2 Oral Exposure

Following gavage administration of ^{14}C-glutaraldehyde to four male Fischer rats at a mean dose of 68.5 mg/kg (Union Carbide Chem & Plas Co. 1991ff), an average of 35% of the administered radioactivity was collected in the feces during 48 hours posttreatment. Lesser amounts of radioactivity were observed in the urine and expired $^{14}CO_2$ (6 and 21% of the administered radioactivity, respectively). Of the expired $^{14}CO_2$, 60% was excreted in the first 6 hours, and 92% was excreted in the first 24 hours. The identity of specific radioactive urinary and fecal compounds was not determined.

3.4.4.3 Dermal Exposure

No information was located regarding elimination or excretion in humans following dermal exposure to glutaraldehyde.

Male and female Fischer 344 rats received aqueous ^{14}C-glutaraldehyde dermally under occluded conditions for 24 hours at concentrations resulting in estimated doses of up to 63–102 mg/kg (McKelvey et al. 1992). Up to 3% of the administered radioactivity was recovered in the urine and lesser amounts in expired $^{14}CO_2$. Anion exchange chromatographic analysis of urine revealed two major fractions comprising 28–41% and 9–14%, respectively, of the urinary radioactivity, and one minor fraction comprising 3–5% of the urinary radioactivity. The chemical composition of the fractions was not determined. For the rats, residual urinary radioactivity was 40–64% of the total urinary radioactivity. Similar administration of ^{14}C-glutaraldehyde to male and female New Zealand white rabbits resulted in elimination of 2–12% and 2–17% of the administered dose in the urine and expired $^{14}CO_2$, respectively. Anion exchange chromatographic analysis of the rabbit urine revealed peaks similar to those obtained from the rat urine, with the exception of a double peak for one of the fractions in the rabbit urine. Major fractions represented 11–25%, and 25–46% and 10–29% (double-peak fraction) of the urinary radioactivity; the minor fraction accounted for 7–9% of the urinary radioactivity. For the rabbits, residual urinary radioactivity was 2–13% of the total urinary radioactivity.

3.4.4.4 Other Routes of Exposure

Male and female Fischer 344 rats received aqueous ^{14}C-glutaraldehyde via intravenous injection (McKelvey et al. 1992). At 24 hours postinjection, approximately 7–12% of the administered dose had been recovered in the urine, 2.5–4.5% in the feces, and 64–78% in expired $^{14}CO_2$. Approximately 24–

33%, 10–29%, and 3–6% of the urinary radioactivity was associated with three separate urinary fractions. The chemical composition of the fractions was not determined; residual urinary radioactivity was 28–53% of the total urinary radioactivity. Following similar administration of ^{14}C-glutaraldehyde to male and female New Zealand white rabbits, approximately 15.5–28%, 0.2–1.5%, and 30–71% of the administered dose were recovered in the urine, feces, and expired $^{14}CO_2$, respectively. Urinary fractions represented 10–19%, 26–44%, and12–20% (double-peak fraction), and 11–16% of the urinary radioactivity. For the rabbits, residual urinary radioactivity was 5–16% of the total urinary radioactivity.

Following intravenous infusion of rats with 10 µCi of ^{14}C-glutaraldehyde, approximately 14% of the dose was collected in the urine during the first hour postinfusion and 29% during the first 6 hours (Ranly and Horn 1990). After 3 days, urinary excretion of radioactivity had decreased to approximately 0.2%/hour. Chromatographic analysis of urinary contents indicated that only 3% of the dose was excreted as parent compound. Specific urinary metabolites of glutaraldehyde were not identified.

Canine and incisor pulpotomy sites of dogs received a cotton pellet containing 5.6 µCi of ^{14}C-glutaraldehyde (as a 2.5% aqueous solution) for 5 minutes (Myers et al. 1986). During 90 minutes posttreatment, radioactivity in urine, feces, and expired air was assessed. Dogs were then sacrificed for assessment of radioactivity in tissues. Approximately 3% of the applied dose was absorbed. Approximately 8% of the absorbed dose was excreted in the urine, another 3.6% in the expired air, and 0.6% in the feces (biliary excretion).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target

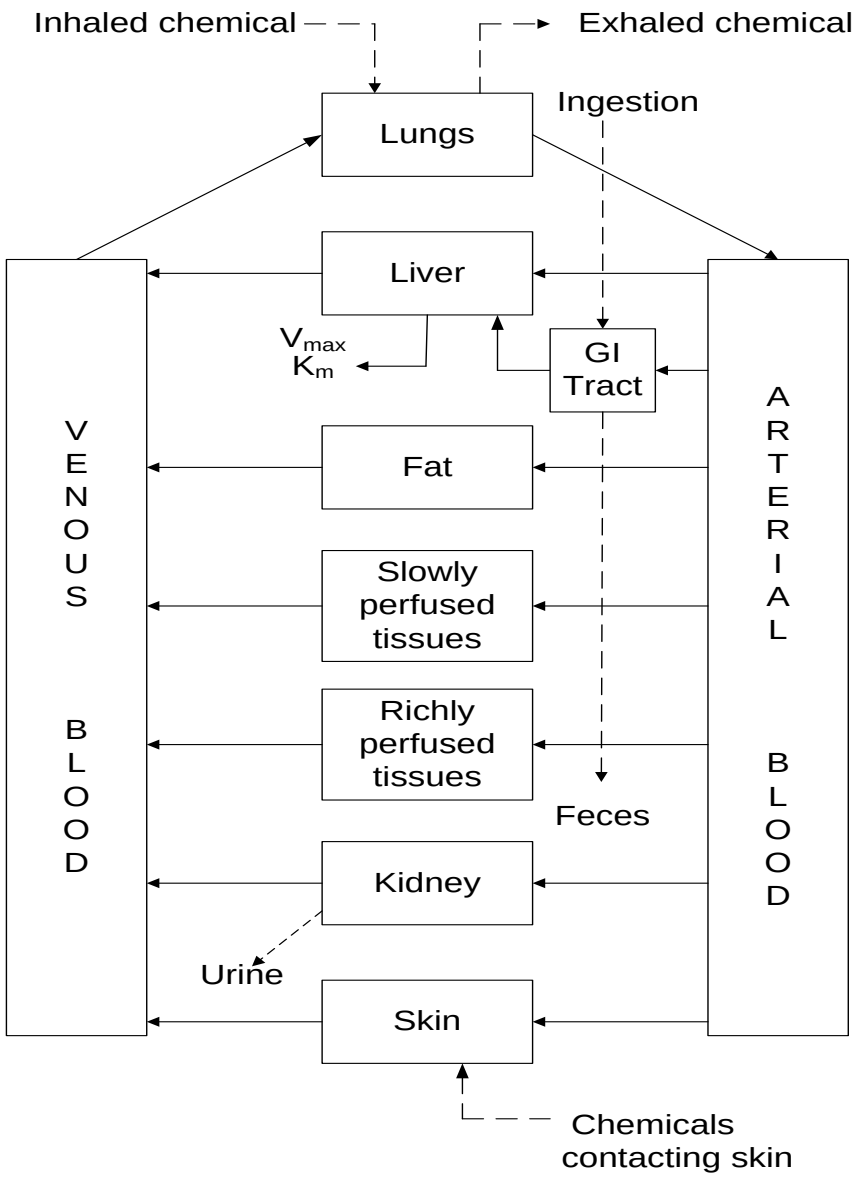
tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

If PBPK models for glutaraldehyde exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models for glutaraldehyde were not located.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No information was located regarding pharmacokinetic mechanisms for glutaraldehyde.

3.5.2 Mechanisms of Toxicity

Aldehydes as a group are reactive chemicals with a highly electronegative oxygen atom and less electronegative atoms of carbon(s), and hence have a substantial dipole moment. The carbonyl atom is the electrophilic site of these types of molecules, making it react easily with nucleophilic sites on cell membranes and in body tissues and fluids such as the amino groups in protein and DNA. The effectiveness of glutaraldehyde as a tanning agent for leather, tissue fixative for microscopy, and biocide is attributed to its propensity to react with and cross-link proteins (Peters and Richards 1977). These molecular properties also contribute to portal-of-entry irritant and cytotoxic effects of glutaraldehyde, although the precise mechanisms for these effects are not known. No information was located regarding possible mechanisms of action for glutaraldehyde-induced dermal sensitization.

3.5.3 Animal-to-Human Extrapolations

Major targets of glutaraldehyde toxicity (portal-of-entry irritation) are common to laboratory animals and humans. Available animal data implicate the kidney as a target of toxicity following oral administration of glutaraldehyde; it is therefore assumed that the kidney is a potential target of toxicity in humans, although no human data were located to support this assumption. No other information was located to indicate major species-specific differences in glutaraldehyde-induced health effects.

3.6 HAZARD IDENTIFICATION AND MINIMAL RISK LEVELS

3.6.1 Hazard Identification

Systematic review of available human and animal studies that assessed potential health effects associated with inhalation, oral, and dermal/ocular exposure to glutaraldehyde resulted in determinations that glutaraldehyde acts as a contact irritant at relatively low exposure levels, causing upper respiratory tract irritation via the inhalation exposure route, gastrointestinal irritation via the oral exposure route, and dermal and ocular irritation upon contact with skin and eyes. Available animal data implicate the kidney as a target of glutaraldehyde toxicity via the oral route of exposure. Hazard identification conclusions for glutaraldehyde, resulting from systematic review of available human and animal data, are presented in Appendix B and are summarized as follows:

- Glutaraldehyde is known to cause irritation of the upper respiratory tract, based on a high level of evidence from human and animal studies.
- Oral exposure to glutaraldehyde is presumed to cause adverse gastrointestinal effects in humans, based on a high level of evidence from animal studies; human data are lacking.
- Direct contact between glutaraldehyde and skin is presumed to cause irritative effects in humans, based on a low level of evidence from human and high level of evidence from animal studies.
- Direct contact between glutaraldehyde and eyes is presumed to cause irritative effects in humans, based a moderate level of evidence from human studies and high level of evidence from animal studies.
- Glutaraldehyde is presumed to cause adverse renal effects in humans, based on a high level of evidence from animal studies that employed inhalation or oral exposure; human data are lacking.

As discussed below, MRLs for glutaraldehyde were derived based on the most sensitive effects from available high quality animal studies.

3.6.2 Minimal Risk Levels (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for glutaraldehyde. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for

acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

3.6.2.1 Inhalation MRLs

Acute-Duration. Limited quantitative human data are available. The glutaraldehyde odor threshold in humans was determined to be in the range of 0.0003 ppm based on multiple 5-second exposures; a similar exposure scenario resulted in a threshold of 0.47 ppm for the perception of an effect on nasal tissue (Cain et al. 2007). Within a group of 50 female subjects exposed to air only or glutaraldehyde vapor at 0.035, 0.050, 0.075, or 0.100 ppm for 15-minute intervals, the cumulative proportion of subjects who achieved 50% correct detection of glutaraldehyde (self-reported perception of nasal sensation) ranged from <5% at the glutaraldehyde concentration of 0.035 ppm to slightly more than 50% at 0.1 ppm (Cain et al. 2007). The threshold of sensory irritation of glutaraldehyde vapor was assessed in five male and four female subjects who had not been regularly exposed to glutaraldehyde vapor (Union Carbide Corp. 1976). The subjects were exposed for 2 minutes/day on 3 consecutive days to vapor from an activated (alkaline) CIDEX solution (2% aqueous glutaraldehyde) and on a 4th day to glutaraldehyde vapor from an unactivated (acidic) solution. Based on self-reported perception of sensory irritation (most frequently nasal irritation; ocular irritation at relatively higher exposure levels), the human sensory irritation threshold was approximately 0.237–0.245 ppm glutaraldehyde from the activated solution and 0.255 ppm for glutaraldehyde from the unactivated solution. Case reports are available regarding glutaraldehyde-induced occupational asthma (Chan-Yeung et al. 1993; Corrado et al. 1986; Cullinan et al. 1992; Di Stefano et al. 1999; Gannon et al. 1995; Ong et al. 2004; Quirce et al. 1999; Trigg et al. 1992); glutaraldehyde challenge concentrations on the order of 0.068–0.075 mg/m^3 (0.016–0.018 ppm) induced hypersensitivity responses in some cases.

Depressed body weight gain and actual body weight loss have been observed in laboratory animals exposed to glutaraldehyde vapor. Single exposure of male and female rats to glutaraldehyde vapor for 4 hours at analytical concentrations in the range of 9.1–43.5 ppm resulted in 35–42% depressed body weight gain during 14 days of postexposure observation (Union Carbide Corp. 1992l). Repeated 6-hour exposures of male and female rats to glutaraldehyde vapor (5 days/week for 11 days) resulted in 33–41% depressed body weight gain at 0.2 ppm glutaraldehyde and 21–22% body weight loss at 0.63 ppm (Union Carbide Corp 1992e).

The occurrence of histopathologic nasal lesions was selected as the critical effect for deriving an acute-duration inhalation MRL for glutaraldehyde because the lesions clearly represent an adverse effect and they occurred in the range of the lowest exposure concentrations employed in available acute-duration inhalation studies. In the study of Union Carbide Corp (1992d), rhinitis and mild atrophy of the olfactory mucosa were observed in male and female F344 rats exposed to glutaraldehyde vapor at 3.1 ppm for 6 hours/day for 9 exposures in 11 days; at an exposure level of 1.1 ppm, males (but not females) exhibited rhinitis and mild squamous metaplasia of the olfactory mucosa. This study identified a no-observed-adverse-effect level (NOAEL) of 0.3 ppm and a lowest-observed-adverse-effect level (LOAEL) of 1.1 ppm for nasal lesions in the male rats. Zissu et al. (1994) observed histopathological lesions in the respiratory epithelium of the septum and naso- and maxilloturbinates of male Swiss OF1 mice exposed to glutaraldehyde vapor for 5 hours/day on 4 consecutive days at 0.3 ppm (the lowest concentration tested); the severity of glutaraldehyde-induced nasal lesions increased with increasing exposure concentration. This study did not identify a NOAEL. In a study designed to evaluate the time course of glutaraldehyde-induced nasal lesions (Gross et al. 1994; NTP 1993), male and female F344 rats and B6C3F1 mice were exposed to glutaraldehyde vapor for 6 hours/day for 1 or 4 days, or 6 or 13 weeks at glutaraldehyde vapor concentrations of 0.0625, 0.125, 0.250, 0.5, or 1 ppm. Exposure-related increased incidences of rats and mice exhibiting selected nasal lesions were observed following exposure to glutaraldehyde vapor at 0.250 ppm 6 hours/day for as little as 1 or 4 days; there were no apparent exposure-related effects on nasal lesion incidences at 0.125 ppm. This study identified a NOAEL of 0.125 ppm and the lowest LOAEL (0.25 ppm for histopathological nasal lesions) among the acute-duration inhalation studies and was therefore selected as the principal study for derivation of an acute-duration inhalation MRL for glutaraldehyde. Benchmark dose (BMD) analysis of nasal lesion incidences is precluded by the small numbers of animals (n=5/sex) evaluated after 1 and 4 days of exposures. Combining the data for males and females within an animal species is not considered appropriate due to uncertainty regarding gender-specific sensitivity to glutaraldehyde-induced nasal lesions and slight gender differences in exposure concentrations resulting in significantly increased incidences of particular nasal lesion types. The

NOAEL of 0.125 ppm and LOAEL of 0.25 ppm for histopathologic nasal lesions (subepithelial neutrophils) in male F344 rats exposed to glutaraldehyde vapor for a single 6-hour period (Gross et al. 1994; NTP 1993) serve as the basis for deriving an acute-duration inhalation MRL for glutaraldehyde. The NOAEL of 0.125 ppm was duration-adjusted to simulate a 24-hour exposure (0.125 ppm x 6 hour/24 hour = $NOAEL_{ADJ}$ of 0.031 ppm) and converted to a human equivalent concentration (HEC; $NOAEL_{HEC}$ = 0.003 ppm) according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde). A total uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for sensitive individuals) was applied and resulted in an acute-duration inhalation MRL of 0.001 ppm ($1x10^{-3}$ ppm). An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for sensitive individuals consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise. Refer to Appendix A for more detailed information regarding derivation of the acute-duration inhalation MRL for glutaraldehyde.

Intermediate-Duration. No adequate exposure-response data are available for humans exposed to glutaraldehyde by the inhalation route.

Exposure-related effects on body weight were observed in rats repeatedly exposed to glutaraldehyde vapor at 0.9–1.6 ppm for periods of 16 days to 13 weeks (NTP 1993; Zissu et al. 1994); as much as 41–42% lower final mean body weight was noted in male and female rats exposed at 1.6 ppm, 6 hours/day for 12 exposures in 16 days. However, the body weight effects may be secondary to effects on the respiratory tract, which appears to be the critical target of glutaraldehyde toxicity following repeated inhalation exposures for 2–13 weeks. Concentration-related increased incidence and severity of clinical signs of respiratory irritation and histopathologic nasal lesions (exfoliation, inflammation, hyperplasia, and ulceration of nasal squamous epithelium; granulocytes and necrosis in nasal passages; laryngeal

squamous metaplasia; necrosis in nasal nares) have been reported at exposure levels as low as 0.0625–1.6 ppm (Gross et al. 1994; NTP 1993, 1999; Union Carbide Corp. 1992f; van Birgelen et al. 2000; Zissu et al. 1998). Histopathologic nasal lesions were sometimes noted at exposure levels lower than those resulting in overt clinical signs of respiratory tract irritation. In general, glutaraldehyde-induced histopathologic respiratory tract lesions were confined to the anterior nasal cavity and were not observed in lower respiratory tract regions. However, in one study that assessed the lung, but not extrapulmonary respiratory tract tissues, morphological changes were observed in pulmonary epithelium of male rats exposed to glutaraldehyde vapor at 0.1 ppm, 6 hours/day, 5 days/week for 4 weeks (Halatek et al. 2003).

Inflammation in the nasal vestibule/anterior nares of the female mice was identified as the most sensitive effect and was observed at the lowest exposure level tested (0.0625 ppm). In a similarly-designed histopathology time-course study that evaluated the progression of nasal lesions for up to 13 weeks (5/species/sex/exposure group/time point) (Gross et al. 1994; NTP 1993), neutrophilic infiltration into intra- and subepithelial regions of the nasal vestibule of female mice was identified as the most sensitive effect and was observed at the lowest exposure level tested (0.0625 ppm). The neutrophilic infiltration was consistent with inflammation in the core study, thus providing support to the findings of the core study. The incidence data for inflammation in the nasal vestibule/anterior nares of the B6C3F1 female mice from the core study (NTP 1993) were selected to serve as the basis for deriving the intermediate-duration inhalation MRL for glutaraldehyde. All dichotomous models in the Benchmark Dose Modeling Software (BMDS, Version 2.2) were fit to the incidence data for female B6C3F1 mice with inflammation in the nasal vestibule/anterior nares following exposure to glutaraldehyde vapor 6 hours/day, 5 days/week for 13 weeks (NTP 1993). A 10% change from control incidence was selected as the benchmark response (BMR). The resulting 95% lower confidence limit on the maximum likelihood estimate of the exposure concentration associated with the selected benchmark response ($BMCL_{10}$) of 0.0034 ppm was adjusted to simulate a continuous exposure scenario (0.0034 ppm x 6 hour/24 hours x 5 days/7 days = $BMCL_{10ADJ}$ of 0.0006 ppm). Derivation of a HEC based on the $BMCL_{10ADJ}$ of 0.0006 ppm was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde), resulting in a $BMCL_{10HEC}$ of 0.00008 ppm ($8x10^{-5}$ ppm). A total uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for human variability) was applied, resulting in an intermediate-duration inhalation MRL of 0.00003 ppm ($3.0x10^{-5}$ ppm). An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of

glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for sensitive individuals consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise. Refer to Appendix A for more detailed information regarding derivation of the intermediate-duration inhalation MRL for glutaraldehyde.

Chronic-Duration. No chronic-duration inhalation MRL was derived for glutaraldehyde. Available human data are inadequate to serve as a basis for a chronic-duration inhalation MRL for glutaraldehyde. 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 (e.g., Jachuck et al. 1989; NIOSH 1987a, 1987b; Norbäck 1988; Pisaniello et al. 1997; Vyas et al. 2000; Waldron 1992; Waters et al. 2003). Case reports of some workers exposed to glutaraldehyde during disinfection processes provide some evidence of glutaraldehyde-induced respiratory hypersensitivity (Chan-Yeung et al. 1993; Corrado et al. 1986; Cullinan et al. 1992; Di Stefano et al. 1999; Gannon et al. 1995; Ong et al. 2004; Quirce et al. 1999; Trigg et al. 1992). In controlled-exposure studies, individuals with diagnosed glutaraldehyde-induced asthma were evaluated for responses to glutaraldehyde challenge exposure (Palczyński et al. 2001, 2005). Other studies found no evidence of glutaraldehyde-induced respiratory sensitization among various groups of hospital workers with exposure to glutaraldehyde (Vyas et al. 2000; Waldron 1992; Waters et al. 2003) or employees at a glutaraldehyde production facility (Teta et al. 1995). However, the available human data do not include quantitative exposure-response information that could potentially serve as a basis for MRL derivation.

Quantitative animal data are available regarding the effects of chronic-duration inhalation exposure to glutaraldehyde. In studies performed for the NTP, male and female F344/N rats (50/sex/group) were exposed whole-body to glutaraldehyde vapor at target concentrations of 0, 0.25, 0.5, or 0.75 ppm for 6 hours/day, 5 days/week for 2 years; male and female B6C3F1 mice (50/sex/ group) were similarly exposed at 0, 0.0625, 0.12, or 0.25 ppm (NTP 1999; van Birgelen et al. 2000). These studies also identified the nasal cavity of the rats and mice as the most sensitive target of glutaraldehyde toxicity and

identified a LOAEL of 0.0625 ppm (the lowest exposure concentration tested) for hyaline degeneration in the respiratory epithelium of the female mice.

To derive a potential chronic-duration inhalation MRL for glutaraldehyde, a NOAEL/LOAEL approach was explored based on hyaline degeneration in the respiratory epithelium of the female B6C3F1 mice because none of the dichotomous models in the Benchmark Dose Modeling Software (Version 2.2) provided adequate fit to the data. Conversion from intermittent exposure to a continuous exposure scenario and calculation of a HEC resulted in a $LOAEL_{HEC}$ of 0.0022 ppm. Application of a total uncertainty factor of 30 (10 for extrapolation from a LOAEL to a NOAEL, 1 for extrapolation from animals to humans using dosimetric adjustment, and 3 for sensitive individuals) to the $LOAEL_{HEC}$ of 0.0022 ppm resulted in a potential chronic-duration inhalation MRL of 0.00007 ppm ($7.0x10^{-5}$ ppm). An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for sensitive individuals consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly; thus, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise. Using a BMD approach and a BMR of 10% change from control incidence for potential derivation of a chronic-duration inhalation MRL based on other nasal lesion incidence data from the male and female rats (squamous epithelial hyperplasia, inflammation) and female mice (respiratory epithelial squamous metaplasia), the lowest $BMCL_{10}$ was 0.025 ppm for squamous epithelial inflammation in the female rats (multistage 1-degree model). Conversion from intermittent exposure to a continuous exposure scenario and calculation of a HEC resulted in a $BMCL_{10HEC}$ of 0.0007 ppm. Application of a total uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for sensitive individuals) to the $BMCL_{10HEC}$ of 0.0007 ppm resulted in a potential chronic-duration inhalation MRL of 0.0002 ppm ($2.0x10^{-4}$ ppm).

The potential chronic-duration inhalation MRL of 0.00007 ppm ($7.0x10^{-5}$ ppm) using a NOAEL/LOAEL approach for hyaline degeneration in the respiratory epithelium of the female B6C3F1 mice is approximately 3-fold lower than the potential chronic-duration inhalation MRL of 0.0002 ppm ($2.0x10^{-4}$ ppm) from the most sensitive effect identified using a benchmark approach ($BMCL_{10}$ of

0.025 ppm for squamous metaplasia in the respiratory epithelium of the F344/N female rats. However, the lowest chronic-duration inhalation MRL of 0.00007 ppm ($7.0x10^{-5}$ ppm) is 2.3-fold higher than the intermediate-duration inhalation MRL of 0.00003 ppm ($3x10^{-5}$ ppm) for inflammation in the nasal vestibule/anterior nares of the B6C3F1 female mice. As a conservative approach, the intermediate-duration inhalation MRL of 0.00003 ppm ($3x10^{-5}$ ppm) is considered to be protective of chronic-duration inhalation exposure to glutaraldehyde.

3.6.2.2 Oral MRLs

No human data are available to serve as a basis for deriving oral MRLs for glutaraldehyde. Animal studies employed gavage or drinking water exposure. Gastrointestinal irritation was commonly observed following bolus gavage dosing; the gastrointestinal tract was less sensitive to glutaraldehyde ingested from the drinking water. It is not likely that humans would inadvertently ingest glutaraldehyde in a bolus dose; therefore, it is not appropriate to derive oral MRLs based on gastrointestinal irritation in animals administered glutaraldehyde by bolus dosing. Humans are not likely to be exposed to toxicologically-significant amounts of glutaraldehyde via the drinking water or diet. However, oral MRLs designed to be protective of possible human consumption of glutaraldehyde-contaminated food or water can be derived based on results of animal studies.

Acute-Duration. No acute-duration oral MRL was derived for glutaraldehyde. Gross pathologic evidence of glutaraldehyde-induced irritation in the lungs was observed following single gavage administration of aqueous glutaraldehyde to rats and mice at doses ≥100 and ≥17 mg/kg, respectively (Ballantyne 1995; Union Carbide Chem & Plas Co. 1992; Union Carbide Corp. 1992i). The respiratory effects are likely the result of aspiration of glutaraldehyde from the stomach.

Significantly depressed mean maternal body weight gain (57% less than controls) was observed in rat dams administered aqueous glutaraldehyde at 50 mg/kg/day during gestation days (GDs) 6–15 (Ema et al. 1992). As much as 19% mean maternal body weight loss was reported in pregnant rabbits administered aqueous glutaraldehyde by gavage during GDs 7–19 at 22.5 mg/kg/day (BASF Corp. 1991a). No treatment-related effects on body weight were seen in male or female rats administered glutaraldehyde in the drinking water for 14 days at concentrations resulting in doses as high as 100–105 mg glutaraldehyde/kg/day (Union Carbide Chem & Plas Co. 1991o).

Developmental end points have been assessed in rats and rabbits following oral exposure of maternal animals during gestation. There was no evidence of glutaraldehyde-induced reproductive or developmental effects following gavage administration of glutaraldehyde at doses as high as 50–68 mg/kg/day during GDs 6–15 (BASF Corp. 1991c; Ema et al. 1992), rats exposed via the drinking water at doses as high as 51 mg/kg/day during GDs 6–16 (BASF Corp. 1990l, 1991b), rabbits administered gavage doses as high as 25 mg/kg/day during GDs 7–19 (BASF Corp. 1990m), or rabbits exposed via the drinking water at doses as high as 23 mg/kg/day during GDs 7–20 (BASF Corp. 1991c). Gavage treatment of pregnant rabbits at 22.5 mg/kg/day resulted in effects that included decreased gravid uterine weight (93% less than controls), decreased number of does with fetuses (1/15 versus 15/15 in controls), increased number of does with 100% resorptions (9/15 versus 0/15 in controls), increased postimplantation loss (94% versus 14% in controls), and markedly reduced mean placental and fetal body weights (BASF Corp. 1991a). However, the 22.5 mg/kg/day dose level was maternally toxic, resulting in death (5/15 does) and actual body weight loss among survivors. Significantly lower mean live fetal body weights (6–9% less than controls) were noted at a gavage dose level of 100 mg/kg/day, a dose that resulted in the death of 5/26 pregnant rats (Ema et al. 1992).

Pathologic evidence of glutaraldehyde-induced gastrointestinal irritation was observed following administration of aqueous glutaraldehyde by single gavage at sublethal and lethal doses to rats and mice (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991t, 1991z, 1992; Union Carbide Corp. 1992a, 1992c, 1992i). Clinical signs of gastrointestinal disturbances (lack of fecal production, diarrhea, and bleeding) were noted in pregnant rabbits administered glutaraldehyde by gavage at 22.5 mg/kg/day during GDs 7–19 (BASF Corp. 1991a). Upper alimentary mucosal irritation was reported for dogs receiving glutaraldehyde from the drinking water for 14 days at 7–10 mg/kg/day (Union Carbide Chem & Plas Co. 1991dd).

Based on available animal data, results of a 14-day oral study in dogs (Union Carbide Chem & Plas Co 1991dd) suggest that the gastrointestinal tract is the most sensitive target of glutaraldehyde toxicity via the oral exposure route. In the study, beagle dogs (2/sex/group) were administered glutaraldehyde (50% w/w aqueous solution) in the drinking water (corrected for percent active ingredient) for 14 days at concentrations of 0, 150, or 250 ppm (author-estimated glutaraldehyde doses of 0, 7, and 14 mg/kg/day, respectively, for the males and 0, 10, and 13 mg/kg/day, respectively, for the females). There were no treatment-related effects regarding clinical signs, body weight, food consumption, clinical chemistry, urinalysis, or necropsy findings. Decreased water consumption was noted in the 250 ppm male and female dogs (approximately 30–45% less than controls). One of two 250 ppm female dogs exhibited

moderate increases in erythrocyte count, hemoglobin, hematocrit, sodium, and chloride; these findings may have been related to mild dehydration. There were no treatment-related organ weight changes. Histopathologic evaluations revealed some evidence of mucosal irritation (glossitis and esophagitis) in the glutaraldehyde-exposed dogs, which was more prominent in the males. The available Toxic Substances Control Act Test Submissions (TSCATS) study summary did not indicate whether the mucosal irritation occurred at both exposure levels; furthermore, insufficient numbers of dogs (2/gender/dose) were used to provide meaningful quantitative analysis of the data.

Intermediate-Duration. No intermediate-duration oral MRL was derived for glutaraldehyde. Available information regarding the effects of intermediate-duration oral exposure of animals to glutaraldehyde is limited. There were no indications of glutaraldehyde-induced respiratory effects in rats or mice receiving glutaraldehyde from the drinking water for 16 days or 13 weeks at doses as high as 100–120 mg/kg/day (rats) and 200–328 mg/kg/day (mice) (Union Carbide Chem & Plas Co. 1991r, 1991v, 1991w). Vomiting was noted in male and female dogs receiving glutaraldehyde from the drinking water for 13 weeks at approximately 10 mg/kg/day; there was no indication of glutaraldehyde treatment-related vomiting in low-dose (ca. 3 mg/kg/day) dogs (Union Carbide Chem & Plas Co. 1991ee). No treatment-related histopathological or hematological effects were observed in studies of rats, mice, or dogs receiving glutaraldehyde from the drinking water for 2–13 weeks at doses as high as 100–120, 200–328, and 13–15 mg/kg/day, respectively (Union Carbide Chem & Plas Co. 1991o, 1991r, 1991v, 1991w, 1991ee). Approximately 12% decreased mean relative kidney weight (in the absence of histopathologic renal lesions) was reported in female rats receiving glutaraldehyde from the drinking water for 16 days at 328 mg/kg/day; kidney weight was not affected in male rats similarly treated at up to 257 mg/kg/day (Union Carbide Chem & Plas Co. 1991v). No treatment-related effects on body weight were seen in male or female rats administered glutaraldehyde in the drinking water for 13 weeks at concentrations resulting in doses as high as 25–35 mg/kg/day; at 100–120 mg/kg/day, depressed body weight gain in male and female rats was the likely result of decreased water and food consumption (Union Carbide Chem & Plas Co. 1991r). In other 13-week drinking water studies, no signs of treatment-related body weight effects were seen among male and female mice at glutaraldehyde doses as high as 200–233 mg/kg/day (Union Carbide Chem & Plas Co. 1991w) or male or female dogs at doses as high as 14–15 mg/kg/day (Union Carbide Chem & Plas Co. 1991ee). There were no signs of ocular effects in rats, mice, or dogs receiving glutaraldehyde from the drinking water for 13 weeks at doses as high as 100–120, 257–327, and 14–15 mg/kg/day, respectively (Union Carbide Chem & Plas Co. 1991r, 1991v, 1991ee).

In a 2-generation oral study, groups of F0 rats were exposed to glutaraldehyde in the drinking water at concentrations resulting in average glutaraldehyde doses of 0, 4.25, 17.5, or 69.07 mg/kg/day for the males and 0, 6.68, 28.28, or 98.37 mg/kg/day for the females; doses to similarly-treated F1 parental rats were 0, 4.53, 21.95, or 71.08 mg/kg/day for the males and 0, 6.72, 29.57, and 99.56 mg/kg/day for the females (Neeper-Bradley and Ballantyne 2000). Significantly depressed mean pup body weight per litter was noted for high-dose F1 pups at postpartum days 21 and 28 (5–11% lower than controls); mean pup body weight gain per litter was 14–19% less than that of controls during lactation days 14–28. Significantly depressed mean pup body weight per litter was noted for high-dose F2 pups at postpartum days 21 and 28 (7–13% lower than controls); for lactation days 14–21 and 21–28, mean pup body weight gain per litter was 17–27% less than that of controls. There were no treatment-related effects on other developmental indices.

Available animal data indicate that the gastrointestinal tract of the dog is the most sensitive target of glutaraldehyde toxicity following intermediate-duration oral exposure. Beagle dogs (4/sex/group; age not specified) were administered glutaraldehyde (50% w/w aqueous solution) in the drinking water (corrected for percent active ingredient) for 13 weeks at concentrations of 0, 50, 150, or 250 ppm (author-calculated glutaraldehyde doses of 0, 3.3, 9.6, and 14.1 mg/kg/day, respectively, for the males and 0, 3.2, 9.9, and 15.1 mg/kg/day, respectively, for the females) (Union Carbide Chem & Plas Co. 1991ee). Increased incidences of intermittent vomiting (fluid and food-like) were observed in the 150 and 250 ppm groups compared to controls and 50 ppm groups. The increased incidences of vomiting are considered to be related to acute irritant properties of glutaraldehyde on the gastric mucosa. The magnitude of body weight changes was reported to be small and without evidence of a clear dose-response. Mean relative kidney weight of the 250 ppm exposure group of female dogs was significantly greater than controls. The increased relative kidney weight in the 250 ppm group of female dogs was not considered biologically significant in the absence of evidence of exposure-related changes in urinalysis or renal histopathology. There were no apparent exposure-related effects regarding hematology or serum chemistry, or results of gross and histopathologic examinations. Results from the 13-week dog study (Union Carbide Chem & Plas Co. 1991ee) are considered inadequate for the purpose of MRL derivation due to the lack of quantitative information in the available study report.

Chronic-Duration. Two chronic-duration oral toxicity animal studies are available for glutaraldehyde. In one study (Confidential 2002; BASF 2013), Wistar rats (50/sex/group) were administered glutaraldehyde (50.5% active ingredient) in the drinking water for up to 24 months at concentrations of 0, 100, 500, or 2,000 ppm (approximate daily glutaraldehyde intakes of 0, 3, 16, and 60

mg/kg/day, respectively, for the males and 0, 5, 24, and 88 mg/kg/day, respectively, for the females). Increased incidences of nonneoplastic lesions were observed at the 2,000 ppm exposure level and involved the larynx (squamous metaplasia in males [18/50 versus 0/50 controls] and females [30/50 versus 0/50 controls]) and trachea (squamous metaplasia in males [4/50 versus 0/50 controls] and females [11/50 versus 0/50 controls]). In addition, significant trends for increasing incidence with increasing glutaraldehyde concentration were noted for diffuse metaplasia in the larynx of male and female rats, focal metaplasia in the larynx of females, focal squamous metaplasia in the trachea of males and females, and diffuse metaplasia in the trachea of females. Metaplasia was nearly always accompanied by accumulation of keratin detritus in the laryngeal and/or tracheal lumen. Some high-dose rats with laryngeal/tracheal metaplasia also exhibited foreign body granulomas in the lung and/or inflammation in the tracheal lumen. Significantly increased incidence of erosion/ulceration was noted in the glandular stomach of 2,000-ppm females. Purulent inflammation in the nasal cavity was seen in three males and six females of the highest exposure level. The 2-year oral toxicity study of glutaraldehyde in Wistar rats (Confidential 2002; BASF 2013) identified NOAELs of 16 and 24 mg glutaraldehyde/kg/day for males and females, respectively, and LOAELs of 60 and 88 mg glutaraldehyde/kg/day for males and females, respectively, based on increased incidences of nonneoplastic laryngeal and tracheal lesions in males and females and increased incidence of erosion/ulceration in the glandular stomach of females.

In the other 2-year oral toxicity study (van Miller et al. 2002), Fischer 344 rats (100/sex/group) were administered glutaraldehyde (50.0–51.3% w/w aqueous solution) in the drinking water at concentrations of 0, 50, 250, or 1,000 ppm for 52 weeks (first interim sacrifice of 10/sex/group), 78 weeks (second interim sacrifice of 10/sex/group), or up to 2 years (main group). Author-reported average glutaraldehyde doses were 0, 4, 17, and 64 mg/kg/day, respectively, for the males and 0, 6, 25, and 86 mg/kg/day, respectively, for the females. Treatment-related effects included slightly depressed body weight and lesions of the stomach. The depressions in body weight were typically <10% in magnitude. Gross pathology revealed gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa) in 250- and 1,000-ppm male and female rats at 52-, 78-, and 104-week sacrifice (prevalences of 30, 10–20, and 10%, respectively) and in animals that died prior to scheduled sacrifice (prevalence of 40%). Histopathology revealed significantly increased incidences of 1,000-ppm male and female rats with mucosal hyperplasia in the stomach at terminal sacrifice (males: 7/51 versus 1/56 controls; females 7/56 versus 1/62 controls), but not at 52- or 78-week interim sacrifices. Incidences of this lesion at the lower dose levels were not significantly different from those of controls. This study identified NOAELs of 4 and 6 mg/kg/day for the male and female rats, respectively, and

LOAELs of 17 and 25 mg/kg/day for male and female rats, respectively, for gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa).

The LOAEL of 17 mg/kg/day for gastric irritation in the male F344 rats (van Miller et al. 2002) is the lowest identified LOAEL from the 2-year studies and is associated with a NOAEL of 4 mg/kg/day. A chronic-duration oral MRL for glutaraldehyde based on the results of the 2-year study in F344 rats can be derived using the NOAEL of 4 mg/kg/day as the point of departure. Application of a total uncertainty factor of 30 (10 for extrapolation from animals to humans and 3 for human variability) results in a chronic-duration oral MRL of 0.1 mg/kg/day. The uncertainty factor for human variability consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly; thus, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise. The chronic-duration oral MRL of 0.1 mg/kg/day is considered protective for acute- and intermediate-duration oral exposure to glutaraldehyde as well.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens

(Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to glutaraldehyde.

No *in vitro* studies were located regarding endocrine disruption of glutaraldehyde.

3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage

may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and

Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information was located to suggest age-related differences in glutaraldehyde toxicity.

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to

identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium).

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts).

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response.

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Glutaraldehyde

No information was located regarding glutaraldehyde-specific biomarkers of exposure, although detection of glutaraldehyde in tissue samples or body fluids could serve as confirmation of exposure to glutaraldehyde.

3.9.2 Biomarkers Used to Characterize Effects Caused by Glutaraldehyde

No information was located regarding glutaraldehyde-specific biomarkers of effects.

3.10 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding interactions of glutaraldehyde with other chemicals.

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to glutaraldehyde than will most persons exposed to the same level of glutaraldehyde in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke).

These parameters result in reduced detoxification or excretion of glutaraldehyde, or compromised function of organs affected by glutaraldehyde. Populations who are at greater risk due to their unusually high exposure to glutaraldehyde are discussed in Section 6.7, Populations with Potentially High Exposures.

Available information regarding potential differences in susceptibility to glutaraldehyde toxicity is limited. Some glutaraldehyde-exposed individuals exhibit dermal sensitization (Bardazzi et al. 1986; Cusano and Luciano 1993; di Prima et al. 1988; Fowler 1989; Hamann et al. 2003; Hansen 1983a, 1983b; Jordan et al. 1972; Kanerva et al. 2000; Kiec-Swierczynska and Krecisz 2001; Kiec-Swierczynska et al. 2001; Kucenic and Belsito 2002; Maibach 1975; Nethercott et al. 1988; Nettis et al. 2002; Ravis et al. 2003; Sanderson and Cronin 1968; Shaffer and Belsito 2000; Stingeni et al. 1995; Tam et al. 1989). Underlying factors contributing to the dermal sensitization of some people, but not others, have not been elucidated.

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to glutaraldehyde. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to glutaraldehyde. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to glutaraldehyde:

Caraccio TR, McGuigan MA. 2004. Formaldehyde and glutaraldehyde. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Williams, 1246-1250.

Leikin JB, Paloucek FP, eds. 2002. Poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 625-626.

Greenberg MI. 2002. Healthcare workers. In: Goldfrank LR, Howland MA, Flomenbaum NE, et al., eds. Goldfrank's toxicological emergencies. 7th ed. New York, NY: McGraw-Hill, 1677-1678.

3.12.1 Reducing Peak Absorption Following Exposure

There are no known methods for reducing absorption of glutaraldehyde following exposure. The following recommendations were extracted from the texts listed above. Glutaraldehyde reacts rapidly with tissues at the portal-of-entry. Prompt removal from the source of exposure is indicated. For

inhalation exposure, move to fresh air; administer humidified oxygen if necessary. Bronchospasm should be treated with standard treatment such as beta-2 agonists. Severe inhalation exposures may require hospitalization for observation and treatment. For dermal and/or ocular exposure, irrigate the exposed area with copious amounts of water. For oral exposure, observe for signs of gastrointestinal effects such as hemorrhage, ulceration, and perforation. In cases involving ingestion of large amounts of glutaraldehyde, central nervous system depression and hypotension may be indicated. In the absence of respiratory compromise, one text indicated that ingested glutaraldehyde may be diluted with water (Caraccio and McGuigan 2004). However, Ballantyne and Jordan (2001) indicated that dilution with water following ingestion of glutaraldehyde solutions might enhance the acute toxicity of glutaraldehyde, based on observations that acute oral LD_{50} values in laboratory animals decreased with increasing dilution down to approximately 1% glutaraldehyde when oral intake was expressed as absolute amount of glutaraldehyde per body weight. Therefore, dilution with water may or may not be advisable, depending on the initial concentration of ingested glutaraldehyde solution. Emesis is contraindicated due to possible caustic injury or central nervous system depression. Activated charcoal should not be administered due to risk of emesis.

3.12.2 Reducing Body Burden

No information was located regarding methods to reduce the body burden of absorbed glutaraldehyde.

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located regarding methods to interfere with the mechanism of action for toxic effects of glutaraldehyde.

3.13 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glutaraldehyde is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of glutaraldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.13.1 Existing Information on Health Effects of Glutaraldehyde

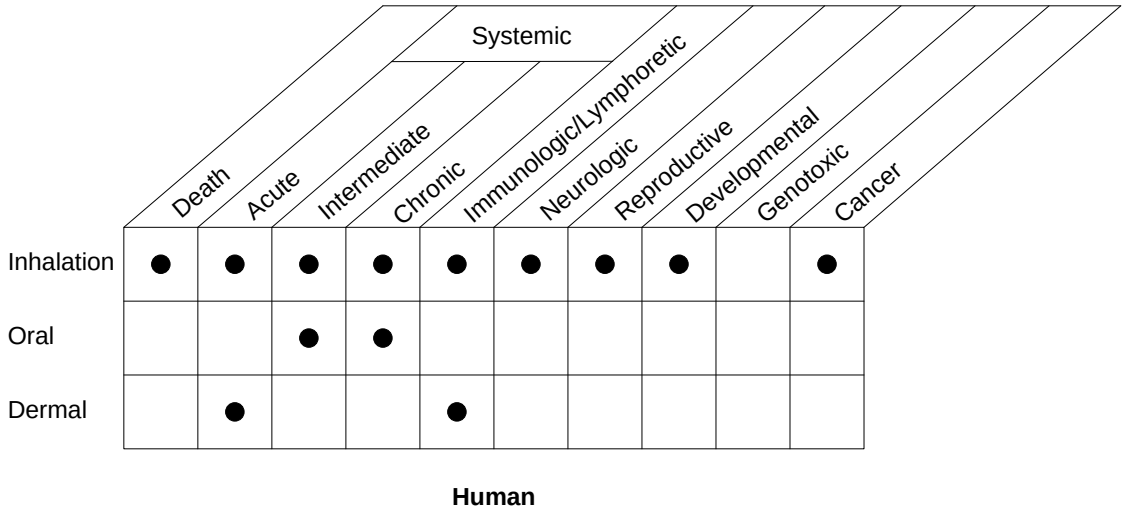
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to glutaraldehyde are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of glutaraldehyde. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

3.13.2 Identification of Data Needs

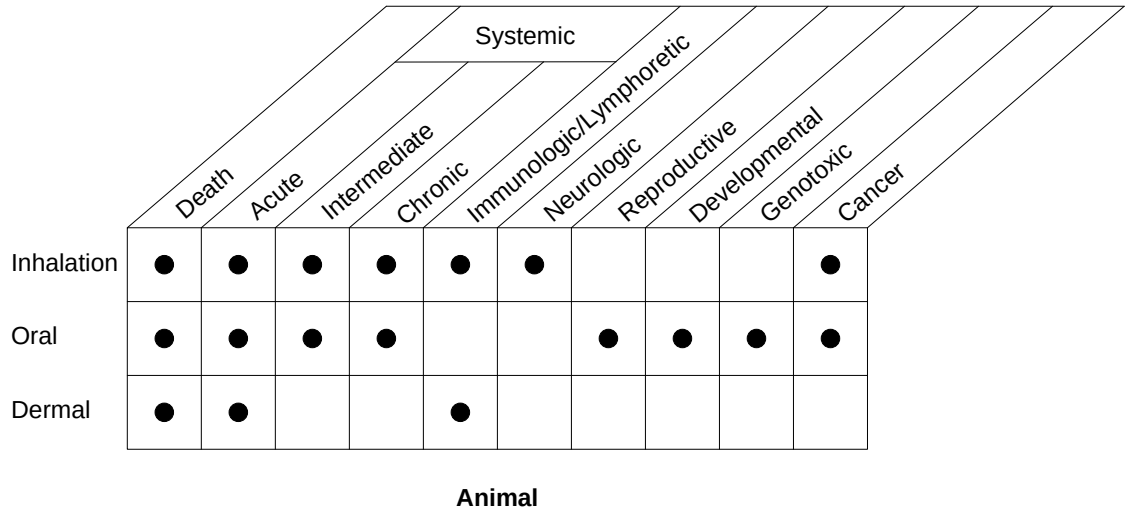
Acute-Duration Exposure. Data are available regarding perception of odor and nasal irritation following acute-duration exposure of volunteers to glutaraldehyde vapor (Cain et al. 2007; Union Carbide Corp 1976). In one controlled human study, repeated occlusive dermal applications of a 0.5% glutaraldehyde solution resulted in application site erythematous responses in 7/109 volunteers and another 9/109 volunteers exhibited questionable responses; similar treatment with 0.1 or 0.2% glutaraldehyde solutions resulted in only three positive results (Union Carbide Corp. 1966). See the section on Epidemiological and Human Dosimetry Studies for a summary of available information regarding occupational exposure to glutaraldehyde.

Sufficient animal data are available regarding the effects of acute-duration inhalation exposure to glutaraldehyde; effects include mortalities at concentrations as low as 1.6 ppm (Zissu et al. 1994) and clinical signs of respiratory tract irritation and histopathologic nasal lesions at concentrations as low as 0.2–2.6 ppm (Ballantyne 1995; Gross et al. 1994; NTP 1993; Union Carbide Corp. 1992d, 1992e, 1992l;

Figure 3-6. Existing Information on Health Effects of Glutaraldehyde



Human



Animal

● Existing Studies

Zissu et al. 1994). Glutaraldehyde-induced histopathologic nasal lesions in rats (Gross et al. 1994; NTP 1993) serve as the critical effect for deriving an acute-duration inhalation MRL for glutaraldehyde. One study found no evidence of glutaraldehyde-induced respiratory sensitization as assessed by the LLNA (van Triel et al. 2011). Other effects in animals acutely exposed to glutaraldehyde vapor include depressed body weight gain and actual body weight loss (Union Carbide Corp. 1992e, 1992l).

The acute oral lethality of glutaraldehyde has been adequately evaluated in laboratory animals using a variety of aqueous dilutions (Ballantyne 1995; BASF Corp. 1990j; Union Carbide Chem & Plas Co. 1992; Union Carbide Corp. 1992b, 1992i). Evaluations of glutaraldehyde dilution on acute lethality in male and female rats and mice indicate greater lethality at dilutions in the range of 1–15% compared to more concentrated solutions (Ballantyne 1995; Union Carbide Chem & Plas Co. 1991l; Union Carbide Corp. 1992i). Maternal deaths were reported from daily gavage administration of glutaraldehyde to rats and rabbits during gestation (BASF Corp. 1991a; Ema et al. 1992). Sublethal effects observed in laboratory animals acutely exposed to glutaraldehyde via the oral route include pathologic evidence of glutaraldehyde-induced gastrointestinal irritation (Ballantyne 1995; BASF Corp. 1991a; Union Carbide Chem & Plas Co. 1991t, 1991z, 1991dd, 1992; Union Carbide Corp. 1992a, 1992c, 1992i) and depressed body weight gain or actual body weight loss (BASF Corp. 1991a; Ema et al. 1992; Union Carbide Chem & Plas Co. 1991v). Available animal data indicate that the gastrointestinal tract in the dog may represent the most sensitive target of glutaraldehyde toxicity via the oral exposure route (Union Carbide Chem & Plas Co 1991dd). However, the available study summary lacked sufficient study details to provide meaningful quantitative analysis of the data. Therefore, no acute-duration oral MRL was derived for glutaraldehyde.

The acute lethality of glutaraldehyde in dermally-exposed animals has been adequately evaluated (Ballantyne 1995; Ballantyne and Jordan 2001; BASF Corp. 1990i; Union Carbide Chem & Plas Co. 1991k, 1991q; Union Carbide Chem & Plas Co. 1991y; Union Carbide Corp. 1992a, 1992b). Glutaraldehyde-induced contact dermal irritation has been observed in numerous animal studies that employed acute-duration exposure (Union Carbide Chem & Plas Co. 1991y; Union Carbide Corp. 1992a, 1992b, 1992c). Signs of immunological effects following dermal induction and challenge exposure to glutaraldehyde include increased mean ear thickness in mice (Azadi et al. 2004; Descotes 1988) and increased lymphocyte proliferation and serum IgE (Azadi et al. 2004; Ballantyne 1995; Hilton et al. 1998; Potter and Wederbrand 1995). Ocular irritation has been reported in laboratory animals following ocular instillation of glutaraldehyde solutions (Ballantyne 1995; Union Carbide Corp. 1992a, 1992b, 1992c; Union Carbide Chem & Plas Co. 1991k; 1991y); ocular irritation has also been observed in animals

exposed to airborne glutaraldehyde (Hoechst Celanese Corp. 1981; Union Carbide Chem & Plas Co. 1991p, 1991x; Union Carbide Corp. 1992e).

Available animal data adequately characterize the hazard of acute-duration exposure to glutaraldehyde via inhalation and dermal routes. Additional animal studies do not appear necessary, but an animal study could be designed to quantitatively assess the sublethal acute oral toxicity of glutaraldehyde in order to provide an adequate basis for deriving an acute-duration oral MRL for glutaraldehyde. Glutaraldehyde-exposed humans should be monitored for signs of glutaraldehyde-induced ocular irritation, nasal lesions, dermal sensitization, and respiratory sensitization.

Intermediate-Duration Exposure. Available data regarding the effects of intermediate-duration exposure of humans to glutaraldehyde are limited to controlled studies of volunteers designed to assess the dermal sensitization potential of glutaraldehyde. In one study, 1/109 subjects exhibited evidence of glutaraldehyde-induced dermal sensitization following repeated dermal applications during induction and subsequent dermal challenge (Union Carbide Corp. 1980). There was no evidence of dermal irritation or sensitization among another group of 21 volunteers following induction and challenge via repeated dermal applications (Union Carbide Corp. 1966). See the section on Epidemiological and Human Dosimetry Studies for a summary of available information regarding occupational exposure to glutaraldehyde.

Intermediate-duration inhalation exposure of rats and mice resulted in clinical signs and histopathologic evidence of respiratory tract irritation (Gross et al. 1994; NTP 1993; Union Carbide Corp. 1992f; Zissu et al. 1998). Glutaraldehyde-induced histopathologic nasal lesions in rats (Gross et al. 1994; NTP 1993) represent an appropriate critical effect from which to derive an intermediate-duration inhalation MRL for glutaraldehyde. There was no evidence of glutaraldehyde-induced respiratory sensitization in a study of guinea pigs repeatedly exposed to glutaraldehyde vapor followed by repeated challenge exposures (Werley et al. 1995).

Depressed body weight gain was reported in male and female rats receiving glutaraldehyde from the drinking water for 13 weeks; however, the effect was the likely result of decreased water and food consumption (Union Carbide Chem & Plas Co. 1991r). Vomiting was noted in dogs receiving glutaraldehyde from the drinking water for 13 weeks (Union Carbide Chem & Plas Co. 1991ee). Available data suggest that dogs may be particularly sensitive to gastrointestinal irritation following oral exposure to glutaraldehyde. However, the only available study summary lacked sufficient study details to

provide meaningful quantitative analysis of the data. Therefore, no intermediate-duration oral MRL was derived for glutaraldehyde.

Increased serum IgE was noted in mice receiving a dermal application of glutaraldehyde followed by a challenge application to the ear (Ballantyne 1995). A questionable response was observed in a similar study (Potter and Wederbrand 1995).

Studies in animals adequately characterize the hazards of intermediate-duration exposure to glutaraldehyde via inhalation. Additional animal studies are needed to quantitatively assess the intermediate-duration oral toxicity of glutaraldehyde in the most sensitive animal species in order to provide an adequate basis for deriving an acute-duration oral MRL for glutaraldehyde. A well-designed intermediate-duration dermal toxicity study in animals is needed to adequately characterize the hazard of repeated dermal exposure to glutaraldehyde.

Chronic-Duration Exposure and Cancer. See the section on Epidemiological and Human Dosimetry Studies for a summary of available information regarding occupational exposure to glutaraldehyde.

Concentration-related increased incidence and severity of histopathologic nasal lesions were noted in rats and mice repeatedly exposed to glutaraldehyde vapor for up to 2 years, (NTP 1999; van Birgelen et al. 2000; Zissu et al. 1998); approximately 10% lower mean body weights were reported in the male and female rats (NTP 1999; van Birgelen et al. 2000). In rats administered glutaraldehyde in the drinking water for up to 2 years, significantly increased incidences of nonneoplastic lesions were noted in the larynx and trachea (Confidential 2002).

Limited data are available regarding the carcinogenicity of glutaraldehyde in humans. Teta et al. (1995) found no evidence of increased mortality from cancer (total malignant neoplasms) within a group of 186 workers assigned to glutaraldehyde production or drumming from 1959 to 1992 at a West Virginia facility when compared to the general U.S. population. A total of 4 cancer deaths were observed compared to 6.1 expected (SMR=0.065; 95% CI: 0.2, 1.7). The cancer SMR was lower for those who worked ≥5 years in the units. Follow-up of this cohort resulted in no evidence for increased cancer rates for respiratory cancers or leukemia (Collins et al. 2006).

NTP determined that there was “no evidence of carcinogenic activity” of glutaraldehyde in male or female F344/N rats exposed to glutaraldehyde vapor at 250, 500, or 750 ppb or male or female B6C3F1 mice exposed to 62.5, 125, or 250 ppb for up to 2 years (NTP 1999). This determination was based on the lack of treatment-related increased incidences of neoplastic lesions in any organ or tissue from the rats or mice. van Miller et al. (2002) reported significantly increased incidences of LGLL in spleens and livers of female (but not male) rats administered glutaraldehyde in the drinking water for up to 2 years at concentrations of 50, 250, or 1,000 ppm (calculated doses in the range of 4–64 mg/kg/day for the males and 6–86 mg/kg/day for the females) (van Miller et al. 2002). 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 among the glutaraldehyde-treated female rats might possibly have been a result of an abnormally low incidence of LGLL in the control females. Upon evaluation of the study results by a Cancer Assessment Review Committee for the U.S. EPA (EPA 2006), it was determined that the incidences of LGLL were either all within the historical range of three studies from the testing laboratory (19–35%) or the NTP historical control database (14–52%). The Committee did not consider the statistically increased incidences of LGLL in the female F344 rats 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 (van Miller et al. 2002), in male or female F344 rats or B6C3F1 mice exposed to glutaraldehyde vapor by inhalation for 2 years (NTP 1999), or Wistar rats exposed via the drinking water for 2 years (Confidential 2002).

Studies in animals adequately characterize the hazards of chronic-duration exposure to glutaraldehyde via the inhalation route and confirm glutaraldehyde-induced nasal lesions as the most sensitive noncancer effect following shorter-term inhalation exposure scenarios. Intermediate-duration inhalation studies employed more exposure levels than chronic-duration inhalation studies, resulting in a slightly more sensitive point of departure. Therefore, the intermediate-duration inhalation MRL is considered protective of chronic-duration inhalation exposure as well. Additional chronic-duration inhalation studies in animals do not appear necessary. Additional information is needed regarding the chronic toxicity and carcinogenicity of glutaraldehyde using oral exposure in animals; noncancer results might serve as a basis for deriving a chronic-duration oral MRL for glutaraldehyde.

Genotoxicity. Available *in vitro* data suggest that glutaraldehyde may be weakly mutagenic in bacteria strains and mammalian cell lines, based on both negative (Haworth et al. 1983; Hemminki et al. 1980; Levin et al. 1982; NTP 1993, 1999; Sakagami et al. 1988a, 1988b; Sasaki and Endo 1978; Slesinski et al. 1983; Vergnes and Ballantyne 2002; Union Carbide Chem & Plas Co. 1991gg, 1991hh, 1991ii; Wilcox et al. 1990) and positive results (Dillon et al. 1998; Haworth et al. 1983; Jung et al. 1992; Kamber et al. 2009; Levin et al. 1982; Marnett et al. 1985; NTP 1993, 1999; Ruiz-Rubio et al. 1985; Vergnes and Ballantyne 2002; Watanabe et al. 1998; Wilcox et al. 1990). There is some evidence for glutaraldehyde-induced chromosomal aberrations, sister chromatid exchange, and micronuclei in mammalian cells systems (Galloway et al. 1985; NTP 1993, 1999; Speit et al. 2008; Tsai et al. 2000). Glutaraldehyde does not appear to cause DNA damage or cell transformation in mammalian cell systems (Speit et al. 2008; Yamaguchi and Tsutsui 2003). Mostly negative results were obtained in assays for glutaraldehyde-induced unscheduled DNA synthesis in mammalian cell systems (Slesinski et al. 1983; St. Clair et al. 1991; Union Carbide Chem & Plas Co 1991gg; Zeiger et al. 2005). Available *in vivo* data do not generally provide support for a genotoxic role for glutaraldehyde; however, data are limited. Glutaraldehyde did not induce DNA cross links and strand breaks, unscheduled DNA synthesis, or dominant lethality in rats and/or mice, or sex-linked recessive lethal mutations in Drosophila (Confidential 1987b, 1987c; Mirsalis et al. 1989; NTP 1993, 1999; Yoon et al. 1985; Zimmering et al. 1989). Negative or equivocal/weakly positive results were reported from assays of glutaraldehyde-induced chromosomal aberrations and micronuclei in mouse bone marrow (Confidential 1987a; NTP 1999; Vergnes and Ballantyne 2002).

Additional *in vivo* genotoxicity studies are needed to adequately assess the genotoxic potential of glutaraldehyde, particularly studies designed to support or refute the evidence of glutaraldehyde-induced chromosomal aberrations and micronuclei in mouse bone marrow cells (NTP 1999).

Reproductive Toxicity. Limited human data are available. Glutaraldehyde exposure did not appear to affect rates of spontaneous abortion among employees at Finnish hospitals compared to control workers at the same hospitals who were not occupationally exposed to sterilizing agents for the years 1973–1979 (Hemminki et al. 1982, 1985). However, the studies included relatively small numbers of spontaneous abortion cases (178 in one study and 217 in another study).

In a well-designed 2-generation reproductive/developmental toxicity study of male and female CD rats administered glutaraldehyde in the drinking water, there were no treatment-related effects on fertility and no histopathological evidence of effects on reproductive organs or tissues (Neeper-Bradley and

Ballantyne 2000). There was no evidence of glutaraldehyde-induced effects on selected reproductive/developmental end points including numbers of corpora lutea, implantation sites, dead implantations, early and late resorptions, or live or dead fetuses, or on gross fetal anomalies at oral doses that did not result in severe maternal toxicity (BASF Corp. 1990l, 1990m, 1991a, 1991b, 1991c, Ema et al. 1992). Sperm morphology and vaginal cytology evaluations in rats and mice repeatedly exposed to glutaraldehyde vapor for 13 weeks revealed no convincing evidence of exposure-related adverse reproductive effects (NTP 1993). No increased incidences of nonneoplastic mammary gland lesions were found in histopathologic evaluations following 2 years of repeated exposure of rats and mice to glutaraldehyde vapor (NTP 1999; van Birgelen et al. 2000).

Although human data are limited, available animal data do not suggest a reproductive toxicity hazard for glutaraldehyde. Additional animal studies are not necessary. Glutaraldehyde-exposed workers should be monitored for potential reproductive effects.

Developmental Toxicity. Available information regarding potential for glutaraldehyde-induced developmental effects in humans is limited to results of a study that included nurses employed in selected departments at Finnish hospitals between 1973 and 1979 with 46 documented cases of mothers with a malformed child and controls consisting of nurses with normal births and matched by age and employment facility (Hemminki et al. 1985). The cases and controls had the potential for exposure to anesthetic gases, cytostatic drugs, and other hazardous substances including glutaraldehyde. One result of the study was the observation that similar proportions of cases with a malformed child and normal birth controls had been exposed to glutaraldehyde (34/164 or 20.7% for cases and 88/464; 19.0% for controls). These results suggest that glutaraldehyde was not likely a causal factor in the malformations, although the small numbers of study subjects precludes any definitive conclusions.

Developmental end points have been assessed in rats and rabbits following oral exposure of maternal animals during gestation. There was no evidence of glutaraldehyde-induced effects on reproductive/ developmental indices including numbers of corpora lutea, implantation sites, dead implantations, early and late resorptions, or live or dead fetuses, or on gross fetal anomalies at doses that did not result in severe maternal toxicity (BASF Corp. 1990l, 1990m, 1991a, 1991b, 1991c; Ema et al. 1992).

In a 2-generation oral study, F1 and F2 pups of maternal rats receiving glutaraldehyde from the drinking water exhibited significantly depressed body weight and body weight gain during postpartum days 14–28,

likely a result of taste aversion to the glutaraldehyde-treated drinking water during weaning (Neeper-Bradley and Ballantyne 2000). There were no treatment-related effects on other developmental indices.

Although human data are limited, available animal data do not suggest a developmental toxicity hazard for glutaraldehyde. Additional animal studies are not necessary. Glutaraldehyde-exposed workers should be monitored for potential developmental toxicity.

Immunotoxicity. Numerous reports are available in which dermal patch testing of glutaraldehyde elicited positive results; these results were obtained for individuals in a variety of occupational settings where glutaraldehyde is used as a germicide (e.g., Bardazzi et al. 1986; Cusano and Luciano 1993; di Prima et al. 1988; Fowler 1989; Hamann et al. 2003; Hansen 1983a, 1983b; Jordan et al. 1972; Kanerva et al. 2000; Kiec-Swierczynska and Krecisz 2001; Kiec-Swierczynska et al. 2001; Kucenic and Belsito 2002; Maibach 1975; Nethercott et al. 1988; Nettis et al. 2002; Ravis et al. 2003; Sanderson and Cronin 1968; Shaffer and Belsito 2000; Stingeni et al. 1995; Tam et al. 1989). In one study designed to assess the dermal sensitization potential of glutaraldehyde in volunteers, repeated dermal applications of glutaraldehyde followed by challenge application resulted in little evidence of glutaraldehyde-induced dermal sensitization (Union Carbide Corp. 1966, 1980).

All groups of mice and the guinea pigs that received dermal applications of 3% glutaraldehyde during induction exhibited visual and radioassay evidence of application-site hypersensitivity upon challenge (Stern et al. 1989). Increased ear thickness was reported in mice following induction and challenge with topical doses of glutaraldehyde (Azadi et al. 2004; Descotes 1988). Repeated dermal applications of glutaraldehyde to the ear of mice resulted in lymphocyte proliferation (Azadi et al. 2004; Hilton et al. 1998). A 4-fold increase in serum IgE was reported for mice receiving dermal application of 25% glutaraldehyde followed by 12.5% glutaraldehyde applied to the ear (Ballantyne 1995). Potter and Wederbrand (1995) reported significantly increased total serum IgE in female BALB/c mice receiving dermal administrations of glutaraldehyde (9.38 mg) on the shaved flank (first application) and dorsal ear (second application), but a higher induction dose (18.75 mg aqueous glutaraldehyde) elicited no increase in total serum IgE. One study found no evidence of glutaraldehyde-induced dermal sensitization in guinea pigs (BASF 2013).

Case reports of some workers exposed to glutaraldehyde during disinfection processes provide some evidence of glutaraldehyde-induced respiratory hypersensitivity (Chan-Yeung et al. 1993; Corrado et al. 1986; Cullinan et al. 1992; Di Stefano et al. 1999; Gannon et al. 1995; Ong et al. 2004; Quirce et al. 1999;

Trigg et al. 1992). Surveys of hospital workers in other studies found no evidence of glutaraldehyde-induced respiratory sensitization (Vyas et al. 2000; Waldron 1992; Waters et al. 2003). There were no indications of glutaraldehyde-induced respiratory sensitization within a group of 218 workers employed at a glutaraldehyde production facility for an average of 3.8 years at TWA glutaraldehyde concentrations generally in the range of 0.04–0.08 ppm, but as high as 1.02 ppm during the year 1982 (Teta et al. 1995).

In one controlled study of health workers with diagnoses of glutaraldehyde-induced occupational asthma and rhinitis, nonexposed atopic subjects with perennial asthma and rhinitis, and nonexposed healthy subjects, glutaraldehyde challenge resulted in significantly increased eosinophil numbers and percentage and significantly increased concentrations of albumin, eosinophil cation protein, and mast-cell tryptase in the nasal lavage fluid among those glutaraldehyde-exposed workers with diagnoses of glutaraldehyde-induced occupational asthma and rhinitis (Palczyński et al. 2001). In a similarly-designed study that evaluated BALF components and Clara cell protein concentration in serum and BALF before and after glutaraldehyde inhalation challenge, postchallenge evaluation revealed significantly lower Clara cell protein levels in BALF and serum at 24 hours postchallenge and significant increases in proportions of eosinophils, basophils, and lymphocytes in BALF of the glutaraldehyde-sensitized asthmatics (Palczyński et al. 2005).

Limited information is available regarding the potential for inhaled glutaraldehyde to cause immunological effects in laboratory animals. There was no evidence of glutaraldehyde-induced respiratory sensitization among male Dunkin-Hartley guinea pigs exposed to glutaraldehyde vapor during induction and challenge phases (Werley et al. 1995). In another study, repeated exposure of BALB/c mice to glutaraldehyde vapor or aerosols resulted in clinical signs of respiratory tract irritation, but no evidence of glutaraldehyde-induced respiratory sensitization as assessed by the local lymph node assay (van Triel et al. 2011).

The potential immunotoxicity of glutaraldehyde has not been adequately assessed; additional human and animal data are needed. Glutaraldehyde-exposed humans should continue to be monitored for dermal and respiratory hypersensivity. Additional animal studies should be designed to further assess the potential for glutaraldehyde-induced hypersensitivity, particularly for the inhalation route of exposure.

Neurotoxicity. Information regarding neurological effects in humans exposed to glutaraldehyde is limited to reports of increased incidences of self-reported headaches among occupationally-exposed

workers during disinfection processes in which glutaraldehyde was used (e.g., Guthua et al. 2001; Norbäck 1988; Pisaniello et al. 1997; Waters et al. 2003).

Impaired righting reflex was noted in rats exposed to glutaraldehyde vapor for 4 hours; decreased motor activity was observed during 14 days of postexposure observation (Union Carbide Corp. 1992l). There were no clinical signs of neurotoxicity in male or female rats or mice repeatedly exposed to glutaraldehyde vapor for 13 weeks (NTP 1993) or rats or mice similarly exposed for up to 2 years (NTP 1999).

Katagiri et al. (2011) measured neurotransmitter levels in various brain regions of the rat following nose-only repeated exposure to glutaraldehyde vapor for 4 weeks. In the medulla oblongata (the only region in which glutaraldehyde exposure-related changes were found), significantly lower mean 5-hydroxyindole-acetic acid content was observed at glutaraldehyde vapor concentrations of 50–200 ppb. Dopamine content was significantly lower at concentrations of 100 and 200 ppm.

Workers exposed to glutaraldehyde vapor during disinfection processes should continue to be monitored for signs of neurological effects. A data need exists for a well-designed neurotoxicity study to assess neurological and neuroendocrine effects in glutaraldehyde-exposed animals. However, because no neurological health effects were observed at concentrations below which nasal lesions were observed, the MRL developed on the basis of nasal lesions should be protective for glutaraldehyde-induced neurological effects.

Epidemiological and Human Dosimetry Studies. Occupational exposure to glutaraldehyde has been commonly associated with symptoms of respiratory tract irritation, dermal irritation, ocular irritation, and headaches, particularly in medical facilities where glutaraldehyde is used as a disinfectant (e.g., Bardazzi et al. 1986; Calder et al. 1992; Cusano and Luciano 1993; di Prima et al. 1988; Fowler 1989; Guthua et al. 2001; Hamann et al. 2003; Hansen 1983a, 1983b; Jachuck et al. 1989; Jordan et al. 1972; Kanerva et al. 2000; Kiec-Swierczynska and Krecisz 2001; Kiec-Swierczynska et al. 2001; Kucenic and Belsito 2002; Maibach 1975; Nethercott et al. 1988; Nettis et al. 2002; NIOSH 1987a, 1987b; Norbäck 1988; Pisaniello et al. 1997; Ravis et al. 2003; Sanderson and Cronin 1968; Shaffer and Belsito 2000; Stingeni et al. 1995; Tam et al. 1989; Vyas et al. 2000; Waldron 1992; Waters et al. 2003). 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 0.012–0.17 ppm (NIOSH 1987a, 1987b; Norbäck 1988; Pisaniello et al. 1997; Vyas et al. 2000). There is some evidence

of glutaraldehyde-induced respiratory hypersensitivity in workers exposed to glutaraldehyde during disinfection processes (Chan-Yeung et al. 1993; Corrado et al. 1986; Cullinan et al. 1992; Di Stefano et al. 1999; Gannon et al. 1995; Ong et al. 2004; Quirce et al. 1999; Trigg et al. 1992); hypersensitivity responses were elicited by challenge exposures as low as 0.016–0.018 ppm. Information regarding acute-duration oral exposure of humans is limited to two case reports of respiratory distress, severe metabolic acidosis, and death in one case following intentional ingestion of biocides consisting of glutaraldehyde and other substances (Perera et al. 2008; Simonenko et al. 2009).

Glutaraldehyde-induced irritative effects have been fairly well documented among humans exposed in occupational settings. However, where potential for human exposure to glutaraldehyde exists, additional data are needed and should include quantitative evaluation of glutaraldehyde-induced symptoms and accurate monitoring of exposure levels to facilitate evaluation of exposure-response relationships. If possible, human studies should include examination of nasal tissue for glutaraldehyde-induced nasal lesions.

Biomarkers of Exposure and Effect.

Exposure. No information was located regarding glutaraldehyde-specific biomarkers of exposure. It is not likely that stable glutaraldehyde-specific biomarkers of exposure could be identified because absorbed glutaraldehyde is rapidly metabolized.

Effect. No information was located regarding glutaraldehyde-specific biomarkers of effects. Classical portal-of-entry irritant effects caused by glutaraldehyde may result from exposure to other highly reactive substances as well. It is not likely that glutaraldehyde-specific biomarkers of effect would be identified.

Absorption, Distribution, Metabolism, and Excretion. No information was located regarding absorption, distribution, metabolism, or excretion of glutaraldehyde or its metabolites following inhalation, oral, or dermal exposure of humans. Limited animal data indicate that glutaraldehyde and/or its metabolites can be absorbed following inhalation exposure (Varpela et al. 1971), oral exposure (Union Carbide Chem & Plas Co. 1991ff), and dermal exposure (McKelvey et al. 1992). Rates of dermal absorption have been estimated based on results of a pharmacokinetic study of rats and rabbits and material balance study in rats (McKelvey et al. 1992). Dermal penetration has been measured across glutaraldehyde-treated skin samples from rats, mice, guinea pigs, rabbits, and humans (Frantz et al. 1993; Reifenrath et al. 1985). Results of animal studies indicate wide systemic distribution following oral or

dermal absorption (McKelvey et al. 1992; Union Carbide Chem & Plas Co. 1991ff). A metabolic pathway for glutaraldehyde has been proposed based on available results from *in vivo* studies and *in vitro* assays (Beauchamp et al. 1992; see Figure 3-4). Limited information is available regarding elimination and excretion following exposure to glutaraldehyde. Following gavage administration of ^{14}C-glutaraldehyde to four male Fischer rats at a mean dose of 86.5 mg/kg (Union Carbide Chem & Plas Co. 1991ff), an average of 35% of the administered radioactivity was collected in the feces during 48 hours posttreatment. Lesser amounts of radioactivity were observed in the urine and expired $^{14}CO_2$ (6 and 21% of the administered radioactivity, respectively). The identity of specific radioactive urinary and fecal compounds was not determined. Following dermal exposure to ^{14}C-glutaraldehyde, up to 3% of the administered radioactivity was recovered in the urine and lesser amounts in expired $^{14}CO_2$. Anion exchange chromatographic analysis of urine revealed two major fractions and one minor fraction. The chemical composition of the fractions was not determined. Similar administration of ^{14}C-glutaraldehyde to male and female New Zealand white rabbits resulted in elimination of 2–12 and 2–17% of the administered dose in the urine and expired $^{14}CO_2$, respectively.

Glutaraldehyde pharmacokinetics have been assessed to some extent in animals. However, a data need exists for additional pharmacokinetic studies in animals to provide support to the proposed metabolic pathways for glutaraldehyde, identify major urinary metabolites, and possibly shed light on mechanisms of action for glutaraldehyde.

Comparative Toxicokinetics. Limited information is available regarding species-specific differences in glutaraldehyde toxicokinetics. Percutaneous absorption of glutaraldehyde and/or its metabolites was greater in rabbits than rats (McKelvey et al. 1992). *In vitro* assessment of dermal penetration indicated somewhat greater penetration in skin from rats, mice, guinea pigs, and rabbits than human skin samples (Frantz et al. 1993). No information was located regarding species-specific differences in distribution or metabolism. Following dermal exposure to glutaraldehyde, the excretion of glutaraldehyde and/or its metabolites in the urine was greater in rabbits than rats; fecal excretion was greater in rats than rabbits (McKelvey et al. 1992).

Portal-of-entry irritation has been identified as the most prominent (and most sensitive) effect of glutaraldehyde toxicity; therefore, large differences in response across species are not anticipated and additional studies in comparative toxicity are not identified as a data need at this time.

Methods for Reducing Toxic Effects. There are no known methods for reducing absorption or body burden of glutaraldehyde following exposure. Glutaraldehyde reacts rapidly with tissues at the portal-of-entry. Prompt removal from the source of exposure is indicated. No information was located regarding methods to interfere with mechanisms of action for toxic effects of glutaraldehyde. It is not likely that additional studies would identify appropriate methods for reducing the toxic effects of glutaraldehyde; therefore, no data need is identified at this time.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No information was located to suggest age-related differences in glutaraldehyde toxicity. Because the most prominent effects of exposure to glutaraldehyde are portal-of-entry irritant effects, it is expected that effects in children would be similar to those observed in adults and laboratory animals. Additional studies that assess potential age-related differences in susceptibility to glutaraldehyde toxicity do not appear necessary.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

No ongoing studies were identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER 2014).

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4. CHEMICAL AND PHYSICAL INFORMATION

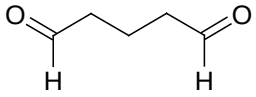
4.1 CHEMICAL IDENTITY

Glutaraldehyde is an aldehyde commonly used as a disinfectant (EPA 2007). Information regarding the chemical identity of glutaraldehyde is located in Table 4-1. Glutaraldehyde is typically prepared as an aqueous solution in which it may exist in various forms depending upon the pH, concentration, and temperature of the solution.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Glutaraldehyde is a colorless, oily liquid with a pungent odor (EPA 2007; HSDB 2011). It is soluble in water and incompatible with strong oxidizers and strong bases (NIOSH 2011). Information regarding the physical and chemical properties of glutaraldehyde is located in Table 4-2.

Table 4-1. Chemical Identity of Glutaraldehyde

Characteristic	Information
Chemical name	Glutaraldehyde
Synonym(s)	Pentanedial; glutaral; glutardialdehyde; glutaric dialdehyde; 1,5-pentanedial; 1,3-diformylpropane; glutaric aldehyde; glutaric acid dialdehyde; glutarol; gluteraldehyde; potentiated acid glutaraldehyde; aldehyd glutarowy (Polish); glutaraldehyd (Czech); glutaralum (INN-Latin); Sporicidin; 4-01-00-03659 (Beilstein Handbook Reference); BRN 0605390; CCRIS 3800; Caswell No. 468; EINECS 203-856-5; EPA Pesticide Chemical Code 043901; NSC 13392; UNII-T3C89M417N[a,b]
Registered trade name(s)	Ucardine; Nuosept 95; Cidex, component of; Odix, component of; Aldesen; Alhydex; Glutaralum; Hospex; NCI-C55425; Sonacide; Coldcide-25 Microbiocide Concentrate; GKN-O Microbiocide Concentrate; Ucarcide 250[b,c,d]
Chemical formula	$C_5H_8O_2$
Chemical structure[a]	
Identification numbers:	
CAS Registry	111-30-8
NIOSH RTECS	MA2450000[e]
EPA Hazardous Waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG	UN 2810[e]
HSDB	949
NCI	No data

[a]ChemIDplus 2013.
[b]HSDB 2011.
[c]McEntee 2000.
[d]EPA 2007.
[e]NIOSH 2011.

CAS = Chemical Abstracts Services; CIS = Chemical Information System; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Glutaraldehyde

Property	
Molecular weight (g/mol)	100.11[a]
Color	Colorless liquid; oily[b]
Physical state	Liquid[a]
Melting point	-14°C[c]
Boiling point	188°C (decomposes)[c]
Density	0.72[c]
Odor	Sharp and pungent[a]
Odor threshold:	
Water	No data
Air	0.0003 ppm; 0.47 ppm for perception of effect on nasal tissue[d]
Taste	No data
Solubility:	
Water	51.3 g/L[a]
Other solvents	Miscible with acetone and isopropanol; methylene chloride = 36 g/L; ethyl acetate = 30 g/L; toluene = 4.4 g/L; n-hexane = 0.096 g/L[e]; soluble in alcohol[c]
Partition coefficients:	
Log K_{ow}	-0.33[b]
Log K_{oc}	120–500[b]
Vapor pressure at 25°C	17 mm Hg at 20°C[c]
OH radical rate constant	2.38×10^{-11} cm^3/molecule-second at 25°C[b]
Henry's law constant at 25°C	2.4×10^{-8} atm-m^3/mol at 25°C (estimated)[b]
Autoignition temperature	No data
Flashpoint	Not applicable[c]
Flammability limits at 25°C	Non-flammable[c]
Incompatibilities	Strong oxidizers, strong bases; alkaline solutions of glutaraldehyde (i.e., activated glutaraldehyde) react with alcohol, ketones, amines, hydrazines, and proteins[f]
Conversion factors (25°C and 1 atm)	1 mg/L=245 ppm; 1 ppm=4.1 mg/m^3[b]
Explosive limits	No data

[a]EPA 2007.
[b]HSDB 2011.
[c]Lewis 2007
[d]Cain et al. 2007.
[e]Ballantyne and Jordan 2001.
[f]NIOSH 2011.

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process glutaraldehyde because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

Glutaraldehyde, one of the most important commercial dialdehydes (Kohlpaintner et al. 2013), is produced by either the gas-phase oxidation of cyclopentene or by a Diels-Alder reaction. In the Diels-Alder reaction, the reaction of acrolein and methyl vinyl ether in a 1:1 ratio results in 3,4-dihydro-2-methoxy-2*H*-pyran (CAS No. 4454-05-1), which undergoes acidic hydrolysis to yield glutaraldehyde and alkanol (HSDB 2011; Kohlpaintner et al. 2013). Both reactions utilize a multistage extraction with water to recover the glutaraldehyde (Kohlpaintner et al. 2013).

Glutaraldehyde is supplied as a 50% biological solution as well as 4, 15, 25, and 45% solutions (EPA 2007; Lewis 2007). It is also available as its bis(sodium bisulfate) adduct (Kohlpaintner et al. 2013). The anhydrous form of glutaraldehyde is unstable and therefore not commercially available (Arntz et al. 2012; EPA 2007).

5.2 IMPORT/EXPORT

Although glutaraldehyde may be imported to the United States from Germany (HSDB 2011; IPCS 1998), actual import volumes were not available. However, it is classified as a High Production Volume (HPV) chemical; HPV chemicals are those chemicals produced or imported to the United States in volumes >1 million pounds (HSDB 2011). Historically, international import volumes of glutaraldehyde are as follows: Australia, over 100 tons/year; Sweden, approximately 165 tons/year; Denmark, approximately 50 tons/year; France, greater than 1,000 tons/year; United Kingdom, several hundred tons/year; and Canada, between 33 and 333 tons/year. Additionally, Norway imports approximately 12,700 tons/year of glutaraldehyde-containing products (IPCS 1998). More recent data were not located.

5.3 USE

Glutaraldehyde is often used in industrial, laboratory, agricultural, and medical settings (Ballantyne and Jordan 2001; EPA 2007). It has numerous uses, including: disinfection and sterilization; leather tanning; chemical intermediate; industrial antimicrobial agent and pesticide (algaecide, bacteriocide, and fungicide); biological tissue fixative; protein and polyhydroxy material cross-linked; 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 (Borchers 2012; EPA 2007; HSDB 2011; IPCS 1998; Kohlpaintner et al. 2013; Lewis 2007). Former uses of glutaraldehyde include cooling tower applications, macrofoulant control, and sterilization of critical medical equipment that would be in contact with bodily fluids (i.e., hemodialysis tubing and dental instruments) (EPA 2007; HSDB 2011).

Glutaraldehyde is often used as a disinfectant for hospital, medical, and dental facilities (EPA 2007). One of the primary uses is for the cold sterilization of medical and dental equipment that cannot be heat sterilized, such as endoscopes or bronchoscopes (Ballantyne and Jordan 2001; Borchers 2012; IPCS 1998; Uhr et al. 2013). Glutaraldehyde can be used to sterilize instruments against a wide spectrum of biocidal activity (both Gram-positive and Gram-negative bacteria, spores, and viruses). Glutaraldehyde is most effective for sterilization around pH 8; however, at this pH, it tends to polymerize. Therefore, it is supplied as a stable, acidic solution (pH 3.0–4.5) and activated by an alkaline buffer (i.e., sodium bicarbonate) to pH 7.8–8.0 (Ballantyne and Jordan 2001; IPCS 1998; Uhr et al. 2013). A 1 or 2% aqueous solution is typically utilized for these applications (Ballantyne and Jordan 2001; IPCS 1998). Glutaraldehyde is also used in x-ray developing solutions as a cross-linking agent to minimize drying time (IPCS 1998).

Glutaraldehyde is often used in industrial settings. In oil and gas recovery and pipeline activities, as well as industrial water treatment, glutaraldehyde may be used as a biocide (API 2015; Arntz et al. 2012; IPCS 1998; Kohlpaintner et al. 2013; McCurdy 2011). Glutaraldehyde is used in a variety of applications for the oil industry, such as in oil storage tanks, water floods, drilling and packer fluids, gas pipe and well systems, and hydrofracturing equipment to prevent growth of sulfate reducing bacteria that contributes to metal corrosion. Glutaraldehyde can also be found in water-based lubricants for conveyors, air washer and industrial scrubbing systems, cooling and process water systems, and sugar beet mills and water systems. In the paper industry, it may be used as a biocide in process water systems, pigments, fillers, and coatings (EPA 2007; IPCS 1998). It is also used in both the paper and textile industries to improve

the wet strength as well as the stability of fibers (Kohlpaintner et al. 2013). Metalworking fluids may also contain glutaraldehyde as an antimicrobial agent (McEntee 2000). In the leather tanning industry, 0.5–2% solutions of glutaraldehyde may be used for leather softening and to help resist mold, water, and alkalis (IPCS 1998).

Agriculturally, glutaraldehyde is used in poultry houses for egg sanitation, cleaning of hatcheries and processing facilities, in animal housing, and for sanitizing farm equipment and other hard surfaces (EPA 2007; IPCS 1998). Typical cleaning solutions contain 0.1–0.3% glutaraldehyde and are sprayed, washed, or foamed onto surfaces. A 400 ppm solution of glutaraldehyde can be used with automated equipment for fogging. Egg shells are sanitized with 750 ppm glutaraldehyde solutions. In aquaculture, glutaraldehyde may be used to help control viruses (IPCS 1998).

In the laboratory, glutaraldehyde is used to cross-link with proteins (Chotani et al. 2012; IPCS 1998). In aqueous solutions, it will partially polymerize, resulting in oligomers (IPCS 1998). It is also used as a bifunctional coupling reagent to bind antibodies to enzymes (Wulff and Henniger 2012) and as a biological tissue fixative (IPCS 1998; Winslow 2003), as well as for the polymerization of pyridoxylated human hemoglobin (Winslow 2003).

The distribution of glutaraldehyde in end-use products for Australia includes: 55% for cold disinfectant for health care settings; 20% for x-ray film processing; 10% for water treatment; 5% for animal housing disinfecting; 5% for tanning of leather; and 5% other (i.e., toilet disinfection, microscopy, aquaculture, and air duct disinfection). In France, the distribution is as follows: 50% for disinfection, 40% for photographic uses, 5% for the leather industry, and 5% for the paper industry. Norwegian usage of glutaraldehyde is primarily for industrial cleaning agents (80%), followed by 14% in photocopying developers. The United Kingdom primarily uses glutaraldehyde for cold disinfectant applications and as a biocide in off-shore oil processes (IPCS 1998). Distribution of use was not available for the United States.

There are limited direct consumer uses of glutaraldehyde, although it may be present in paints and laundry detergents as a slimicide (EPA 2007; HSDB 2011). It is used to sanitize hard surfaces in areas that the general population may encounter (EPA 2007). It may also be present as a preservative in non-aerosol cosmetics in the European market at concentrations <0.1% (IPCS 1998; McEntee 2000). Use of glutaraldehyde as a pesticide for food use is prohibited (EPA 2013g). Glutaraldehyde may have been

used for the topical treatment of warts (i.e., plantar warts) (HSDB 2011), although it is generally not used on skin (Siebert and Harke 2012).

Counterfeit products advertised as glutaraldehyde, but containing substitutes such as formaldehyde and/or other aldehydes, may be found in some markets (McGinley 2012). Toxicity profiles of such products may be significantly different from that of genuine glutaraldehyde; counterfeit products may also be difficult to distinguish from genuine glutaraldehyde without the assistance of sophisticated analytical procedures.

5.4 DISPOSAL

Glutaraldehyde is considered toxic to fish, aquatic invertebrates, oysters, and shrimp and should not be discharged to water bodies (EPA 2007; IPCS 2000; NIOSH 2000). It is subject to requirements under the National Pollution Discharge Elimination System (NPDES) (EPA 2007).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Glutaraldehyde is used as a biocide in medical, industrial, agricultural, oil and natural gas industry, and laboratory settings (Ballantyne and Jordan 2001; EPA 2007). It can be released to the environment through various means. It may enter indoor air from its uses as a disinfectant, in x-ray development, and from paints and laundry detergents that used it as a slimicide (EPA 2007; HSDB 2011; Rietz 1985; Sekine et al. 2005). Glutaraldehyde can also enter the atmosphere from oil and gas operations, industrial water treatment processes, poultry house fogging, and vehicle emissions (Arntz et al. 2012; EPA 2007; HSDB 2011; IPCS 1998; Kohlpaintner et al. 2013).

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 (Arntz et al. 2012; EPA 2007; IPCS 1998; Kohlpaintner et al. 2013). Glutaraldehyde solutions are often disposed of as sewage, from which residues can be released to water following sewage treatment processes (IPCS 1998). Disposal of cold disinfectant solutions from hospitals is the major source of glutaraldehyde to surface waters (Emmanuel et al. 2005; IPCS 1998; Jolibois et al. 2002).

When in the environment, glutaraldehyde is generally in the aquatic phase. Glutaraldehyde degrades rapidly under both aerobic and anaerobic conditions in water and under aerobic conditions in soil (EPA 2007; Leung 2001). It is considered to be rather mobile in soils (HSDB 2011). Glutaraldehyde does not bioaccumulate in aquatic organisms, and is not thought to present a significant risk to aquatic or terrestrial compartments (HSDB 2011; IPCS 1998). Glutaraldehyde solutions are most stable under acidic to neutral conditions (Ballantyne and Jordan 2001; EPA 2007; IPCS 1998; Smith and Wang 2006; Uhr et al. 2013). Higher pH levels can cause it to polymerize over time (Smith and Wang 2006).

Glutaraldehyde has been identified in both indoor and outdoor air samples (Ban-Weiss et al. 2008; HSDB 2011; NICNAS 1994; Rietz 1985; Sekine et al. 2005). The majority of the atmospheric monitoring has been done in hospitals and dental clinics where glutaraldehyde is used for sterilization. The highest airborne concentrations generally occur near the source of sterilization equipment, although the effects are often mitigated by proper ventilation and handling techniques (Rietz 1985). Concentrations of glutaraldehyde in wastewater have been measured, primarily for waste streams originating from hospitals where glutaraldehyde solutions are regularly disposed of as sewage (Jolibois et al. 2002).

Exposure to glutaraldehyde is primarily through inhalation (Smith and Wang 2006), although dermal contact and ingestion may also occur (NIOSH 2000, 2011). The general public is generally not exposed to glutaraldehyde, as it is primarily used in industrial or medical applications (EPA 2007; IPCS 1998). 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 (EPA 2007; IPCS 1998). There is a slight potential for glutaraldehyde residues to contaminate food sources due to its use as a disinfectant in animal housing (EPA 2007). The primary occupational exposure to glutaraldehyde occurs when products are used in medical and dental applications for disinfecting purposes or x-ray processing (EPA 2007; HSDB 2011; IPCS 1998; NICNAS 1994; Smith and Wang 2006). Operating room nurses, radiographers, x-ray technicians, and cleaning staff have the highest potential for glutaraldehyde exposure (Smith and Wang 2006). However, occupational exposure may also occur as a result of paper manufacturing, oil and gas operations, animal house fogging and cleaning, metalworking, and other industrial processes where glutaraldehyde is used or produced (EPA 2007; IPCS 1998).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

There is no information on releases of glutaraldehyde to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glutaraldehyde may be released to indoor air from its used as a disinfectant (EPA 2007; Rietz 1985). Glutaraldehyde is used in hospitals and dental clinics as a disinfectant as well as in the process of developing x-rays, where it has been identified in air samples (Rietz 1985; Sekine et al. 2005). Releases to air can also occur from the use of paints and detergents that contain glutaraldehyde as a slimicide (EPA 2007; HSDB 2011). Levels of glutaraldehyde in indoor air can typically be controlled with proper use and ventilation practices (Rietz 1985).

Releases of glutaraldehyde to outdoor air can occur from its use as a biocide in oil and gas recovery and pipeline operations, as well as industrial water treatment (Arntz et al. 2012; IPCS 1998; Kohlpaintner et al. 2013). Poultry house fogging can also release glutaraldehyde to the air (EPA 2007; IPCS 1998). Glutaraldehyde can also be released to air from vehicle emissions (HSDB 2011). As might be expected, medium and heavy duty diesel trucks were found to contribute more glutaraldehyde to the atmosphere than light-duty vehicles (HSDB 2011).

6.2.2 Water

There is no information on releases of glutaraldehyde to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glutaraldehyde may be released to water as a result of its many commercial and industrial uses, including applications as a biocide in industrial water treatment processes, textile and paper industries, cooling and process water systems, oil and gas operations (including hydrofracturing processes), x-ray processing, and leather tanning (API 2015; Arntz et al. 2012; EPA 2007; IPCS 1998; Kohlpaintner et al. 2013; McCurdy 2011). Waste solutions of glutaraldehyde are typically poured down the drain and thus enter sewage treatment facilities. Treated sewage effluent is then released to surface waters, allowing glutaraldehyde residues to enter the aquatic environment (IPCS 1998).

The use of glutaraldehyde in disinfectants can result in significant release of glutaraldehyde to surface waters (Emmanuel et al. 2005; EPA 2007; IPCS 1998; Jolibois et al. 2002; Sano et al. 2005). In particular, disinfectants from facilities such as from hospitals are discharged to waste water, often in large quantities, which can then enter water resources where they may present a risk to aquatic organisms (Emmanuel et al. 2005; Jolibois et al. 2002). Its use as a cold disinfectant in hospitals, particularly in metropolitan areas, results in large quantities of glutaraldehyde being released to sewage, and it was found that these solutions may retain at least 50% of their biocidal activity (IPCS 1998). Australian data

indicate that the primary release of glutaraldehyde to the environment arises from its use as a cold sterilant, which is released to sewage. Assuming that 75% of the 50 tonnes per year of glutaraldehyde used for cold sterilization is disposed of in sewage in a worst-case scenario, the average daily Australian discharge of glutaraldehyde would be 100 kg, resulting in a wastewater concentration of approximately 40 µg/L (IPCS 1998).

Jolibois et al. (2002) predicted that the glutaraldehyde concentration in hospital waste water is 0.50 mg/L, due to disinfecting solutions being released to aquatic environments after use. However, upon measurement of glutaraldehyde concentrations at Rouen University Hospital, it was discovered that peak glutaraldehyde concentrations in waste water were around 8 times higher than predicted. The hospital uses approximately 10 m^3 (10,000 L) of glutaraldehyde-containing solutions per year, containing approximately 365 kg of glutaraldehyde. Measured glutaraldehyde concentrations in the hospital waste water were typically around or below the predicted concentration of 0.5 mg/L, with the exception of one sample, where the glutaraldehyde concentration was 3.72 mg/L. This sample was found to correlate to when disinfecting solutions were replaced within the hospital, and the remaining solution from the previous week was discarded (Jolibois et al. 2002).

Waste water originating in hospitals can contain hundreds of hazardous chemicals (Emmanuel et al. 2005). Interactions between these chemicals can have additional consequences in the environment, such as the combination of glutaraldehyde from disinfectants with surfactants, chemicals commonly contained in detergents (Emmanuel et al. 2005). A study of the release of glutaraldehyde from waste water to water resources determined that it is acutely toxic on aquatic organisms (Emmanuel et al. 2005). It may be considered moderately toxic to aquatic organisms and highly toxic to algae (Jolibois et al. 2002), although it appears that in many situations, dilution mitigates the risk to the aquatic environment (IPCS 1998). The risk to the aquatic environment, particularly algae, may be higher during periods of drought (IPCS 1998). Additionally, biodegradation and reaction with proteinaceous constituents of raw sewage may help to mitigate glutaraldehyde concentrations in waste water (IPCS 1998).

Smaller volumes and concentrations of glutaraldehyde are typically used in applications other than cold sterilization. X-ray film processing may not present a significant hazard to the aquatic environment as glutaraldehyde reacts with sulfites in the process. For cooling water discharge, Australian data indicate that glutaraldehyde is released to sewage at maximum concentrations of 250 mg/L. Leather tanning is expected to result in discharge of 1–3% of the original amount glutaraldehyde, which may then react with dissolved proteins in the effluent from the tannery. As animal housing typically results in release to the

atmosphere through spraying, it is not expected to contribute significantly to aquatic glutaraldehyde contamination. In Sweden, waste water emanating from paper mills can contain glutaraldehyde at concentrations of 6 mg/L (IPCS 1998).

Glutaraldehyde has been investigated for use as a biocide in ballast water treatment for both marine and freshwater systems (U.S. Coast Guard 2004). In this capacity, there is a significant likelihood of release to water (Sano et al. 2005). A study of biocides for ballast water noted that after treatment, some residual glutaraldehyde could remain in water (U.S. Coast Guard 2004). Despite its release potential, glutaraldehyde appears to be an effective biocidal treatment against a wide range of organisms for this application (U.S. Coast Guard 2004). It was noted that glutaraldehyde is a Class D substance under the Merchant Shipping Regulations (Control of Pollution by Noxious Liquid Substances in Bulk), Schedule I (1987) for Great Britain, under which discharge into the sea is prohibited and discharge of residual mixtures is subject to restrictions. Glutaraldehyde is also regulated under OSHA (U.S. Coast Guard 2004). Regardless, since it was found to have relatively quick half-life in water (<2 days) and has limited regulatory concerns, the study found that glutaraldehyde has a potential for use in ballast water treatment (U.S. Coast Guard 2004), and can thus enter the aquatic environment.

6.2.3 Soil

There is no information on releases of glutaraldehyde to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glutaraldehyde use in disinfectants could result in release to soils and sediments (EPA 2007; IPCS 1998) through release of waste water that may leach into surrounding soils. Likewise, glutaraldehyde could potentially be released to soil as a result of industrial uses, including industrial water treatment processes, paper and textile industries, cooling and process water systems, and oil and gas recovery operations (Arntz et al. 2012; EPA 2007; IPCS 1998; Kohlpaintner et al. 2013). However, as glutaraldehyde is a hydrophilic compound, biodegrades in soil, and does not bioaccumulate, it does not appear to present a risk to the terrestrial environment (IPCS 1998).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

In the environment, glutaraldehyde is expected to partition to water, due to small air/water and soil/water partition coefficients. It degrades under both aerobic and anaerobic conditions in water and under aerobic conditions in soil (EPA 2007). Due to the limited persistence in air, soil, and water, significant transport of glutaraldehyde is not expected (IPCS 1998). If glutaraldehyde is present in soil and sediments, however, it is not expected to significantly adsorb (Emmanuel et al. 2005; HSDB 2011), but could potentially be mobile. A study was performed to determine the adsorption and desorption potential of glutaraldehyde in various soil types. Aqueous solutions of glutaraldehyde in 0.01 M calcium chloride at concentrations of 0.51, 1.0, 2.5, 5.0, and 10.3 g/L were used to determine measured K_{oc} values in different soil types. K_{oc} values of glutaraldehyde in sandy loam, silty clay loam, silt loam, loamy sand, and sediment were determined to be 210, 500, 340, 460, and 120, respectively. These results indicate that glutaraldehyde has a moderate to high mobility in soil, and will therefore not adsorb strongly (HSDB 2011). In particular, glutaraldehyde has a high mobility in sandy soil, but a more moderate mobility in sandy loam, silt loam, silty clay loam, and loamy sandy soils (EPA 2007). Based on an estimate Henry's Law constant of $2.4x10^{-8}$ atm-m^3/mole, glutaraldehyde is not expected to volatilize from water surfaces (HSDB 2011). It also has a low likelihood of volatilizing from either moist or dry soil (HSDB 2011).

6.3.2 Transformation and Degradation

Glutaraldehyde is a hydrophilic compound and is considered to be readily biodegradable in both water and soil (EPA 2007; HSDB 2011; IPCS 1998; Jolibois et al. 2002; Leung 2001). It is not expected to bioaccumulate in aquatic organisms at an appreciable rate (HSDB 2011; IPCS 1998), based on an estimate bioconcentration factor (BCF) value of 3.2 (HSDB 2011). The risk to aquatic organisms is thought to be low under typical, non-drought conditions and there are no appreciable risks to the terrestrial environment from release of glutaraldehyde (IPCS 1998).

Glutaraldehyde is stable under acidic to neutral conditions (EPA 2007). The anhydrous form of glutaraldehyde is unstable, and therefore, it is only available commercially as a solution (Arntz et al. 2012; EPA 2007; Lewis 2007). While glutaraldehyde is stable in light, it oxidizes in the presence of air (Smith and Wang 2006). Additionally, increasing temperature and pH results in decreased stability for aqueous glutaraldehyde solutions (Smith and Wang 2006). While glutaraldehyde solutions are stable at acidic pH, they are only useful as disinfectants at alkaline pH levels (Thomas and Russell 1974).

Glutaraldehyde tends to polymerize around pH 8–9, which coincides with the pH where it is most effective as a disinfectant. It is, therefore, supplied as a stable, acidic solution of pH 3.0–4.5 and must be activated by an alkaline buffer such as sodium bicarbonate to pH 7.8–8.9 before use (Ballantyne and Jordan 2001; IPCS 1998; Smith and Wang 2006; Uhr et al. 2013). Dilute glutaraldehyde solutions (1–2%) are typically used for disinfecting, but they tend to polymerize with time, resulting in a solution containing limited aldehyde radicals and consequently reduced antibacterial function. Glutaraldehyde solutions must, therefore, be prepared fresh on a regular basis (Smith and Wang 2006).

6.3.2.1 Air

Small amounts of glutaraldehyde that volatilize to air (for example, from water cooling tower drift due to its use as a biocide in cooling systems) will not likely persist in the atmosphere. It is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals. For this reaction, it has an estimated half-life in air of 16 hours. As glutaraldehyde has an experimental first-order rate constant of 0.0035/day for the photolysis of aqueous solutions, it may be susceptible to direct photolysis by sunlight (HSDB 2011; IPCS 1998). Additionally, glutaraldehyde is hydrophillic and will be removed from the atmosphere by wet deposition (IPCS 1998).

6.3.2.2 Water

Glutaraldehyde is expected to quickly decompose in water (Emmanuel et al. 2005; EPA 2007; IPCS 1998; Leung 2001; U.S. Coast Guard 2004), and has been classified as readily biodegradable in freshwater, as determined by the Organization for Economic Cooperation and Development (OECD) 301D (Closed Bottle) method, with the potential for degradation in marine environments. Glutaraldehyde present at 100 mg/L, achieved 59% of its theoretical biochemical oxygen demand (BOD) using an activated sludge inoculum and the modified MITI (OECD 301C) test (HSDB 2011).

A study performed using a river water-sediment system found that glutaraldehyde degraded rapidly under both aerobic and anaerobic conditions. In this system, glutaraldehyde was found to partition primarily to the water phase, with a pseudo-first-order half-life of 10.6 hours under aerobic conditions and 7.7 hours under anaerobic conditions (Leung 2001). Glutaraldehyde was stable in sterilized control samples maintained at pH 5 and 7 for 31 days; however, at pH 9, 30% was degraded, primarily to a cyclicized dimer of glutaraldehyde, 3-formyl-6-hydroxy-2-cyclohexene-1-propanal. Extrapolated half-lives for abiotic degradation of 508, 102, and 46 days at pH 5, 7, and 9, respectively were calculated. Under aerobic conditions, glutaraldehyde was found to degrade to glutaric acid and subsequently carbon dioxide,

whereas under anaerobic conditions, it was degraded into 5-hydroxypentanal followed by 1,5-pentanediol (Leung 2001). A second study from the EPA Registration Eligibility Decision (RED) document for glutaraldehyde reported hydrolysis half-lives at 25°C of 628, 394, and 63.8 days at pH 5, 7, and 9, respectively (EPA 2007). At 70°C, hydrolysis of glutaraldehyde proceeds more rapidly with half-lives of 53, 6.5, and 0.23 days at pH levels of 5, 7, and 9, respectively. Glutaraldehyde was also photolytically degraded to a small degree in natural sunlight at 25°C. The half-life was calculated to be 195 days. A buffered, aqueous solution at pH 5 was used in the experiment (EPA 2007).

Since glutaraldehyde is a biocide, it is toxic to many aquatic organisms (Emmanuel et al. 2005; NIOSH 2000). However, Emmanuel et al. (2005) concluded that glutaraldehyde release in hospital waste water at typical concentrations ranging from 0.50 to 3.72 mg/L would not likely pose a threat to beneficial bacteria in waste water treatment processes (Emmanuel et al. 2005). Glutaraldehyde present at 100 mg/L, achieved 59% of its theoretical BOD using an activated sludge inoculum and the modified MITI (OECD 301C) test (HSDB 2011).

Contamination of groundwater and surface waters by glutaraldehyde is unlikely due to rapid biodegradation potential and dilution in surface waters (EPA 2007; IPCS 1998). Degradation of glutaraldehyde in sewage treatment plants, where it reacts with proteins in the effluent, is expected to help mitigate release to water (IPCS 1998). Dilution may also have a significant effect on glutaraldehyde concentrations in water. Studies at a Canadian paper mill and a de-inking plant showed rapid reductions in glutaraldehyde concentrations in white water effluent (water that is removed from paper-processing systems during formation of paper sheets, filtered, and reused within several seconds or minutes to reduce the need for fresh water). After 6 hours, the glutaraldehyde concentration in white water effluent from the paper mill was reduced from 51 to 4 mg/L. At the de-inking plant, glutaraldehyde concentrations in effluent was reduced from 56 to 5 mg/L in 7 hours. The study concluded that dilution was a contributing factor in decreasing the glutaraldehyde concentrations (IPCS 1998).

6.3.2.3 Sediment and Soil

Glutaraldehyde does not appear to present any appreciable risks when released to the terrestrial environment due to its adsorption coefficients, tendency to partition to water, and biodegradation potential. It is expected to have limited persistence in soil (EPA 2007; IPCS 1998).

When present in soil and sediments, it is not expected to adsorb significantly and will have a moderate to high mobility (Emmanuel et al. 2005; EPA 2007; HSDB 2011), based on measured K_{oc} values ranging from 120 to 500 (HSDB 2011). The high mobility indicates that glutaraldehyde may not be present in significant quantities in soil. It has been found to rapidly degrade in soils under aerobic conditions (EPA 2007). Leung (2001) found that glutaraldehyde was metabolized rapidly under both aerobic and anaerobic condition in a water-sediment system.

6.3.2.4 Other Media

No information was located regarding the transformation and degradation of glutaraldehyde in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to glutaraldehyde depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of glutaraldehyde in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on glutaraldehyde levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring glutaraldehyde in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Glutaraldehyde was found to be released to air from vehicle emissions. Measurements taken in a San Francisco Bay area highway tunnel during the summers of 2001 and 2006 found mean emission factors from light-duty vehicles of 0.13 and 0.06 mg glutaraldehyde/kg gasoline, respectively. Glutaraldehyde was not detected in samples from 1999. Medium- and heavy-duty diesel trucks were found to emit more glutaraldehyde to the atmosphere than light-duty vehicles; in 2006, a mean emission factor of 0.55 mg glutaraldehyde/kg diesel was measured in the tunnel (Ban-Weiss et al. 2008). Light-duty vehicles and medium/heavy-duty diesel trucks passed through separate bores of the tunnel.

Sampling was performed at three Danish hospitals and a dental clinic to determine the concentrations of glutaraldehyde in air in facilities where it is used for disinfection of endoscopes and in the development of x-rays. Air samples obtained over 15–25-minute time periods found concentrations of glutaraldehyde

ranging from <0.080 to 0.500 mg/m^3 (<0.02–0.12 ppm) of air. Levels in the hospital settings were higher than those in the dental clinic, where glutaraldehyde is primarily used for x-ray development. In the hospital samples, the highest levels of airborne glutaraldehyde were found in the surgical department. According to the authors, the low glutaraldehyde concentrations found in these facilities are likely a result of proper handling and ventilation practices (Rietz 1985).

A dental clinic in Kanagawa, Japan that utilizes a glutaraldehyde solution for equipment sterilization was monitored for airborne glutaraldehyde concentrations. Eight-hour samples were collected using a passive sampler when the dental clinic was closed, such that the wind speeds during sampling were constant. Samples were obtained at 1.2 m above the floor, at the typical breathing height of a Japanese adult. Indoor air concentrations ranged from not detectable to 16 ppb. The highest concentrations were located in the examination room, nearest the sterilizer, whereas glutaraldehyde was not detectable in the waiting room (Sekine et al. 2005).

Australian studies of glutaraldehyde in air during cold disinfection practices found that concentrations rarely exceeded 0.1 ppm when proper ventilation procedures were followed (NICNAS 1994). Monitoring of Australian hospitals near endoscopy areas where glutaraldehyde was used in 1–2% solutions, using both personal and area monitoring equipment, found air concentrations ranging from 0 to 0.49 ppm, while operating room measurements ranged from 0 to 0.9 ppm. Monitoring at dental facilities resulted in air concentrations ranging from 0.007 to 0.022 ppm. Other hospitals were found to have personal glutaraldehyde monitoring air concentrations up to 0.6 ppm and area monitoring concentrations of up to 0.3 ppm (NICNAS 1994). Air concentrations of glutaraldehyde in areas where x-ray film is processed were generally <0.2 ppm in Australia. The air concentrations ranged from 0 to 0.4 ppm (NICNAS 1994). In an Australian chicken farm, air concentrations were found to be 0.007 ppm when an egg collector sprayed 0.1–0.3% glutaraldehyde solutions (NICNAS 1994).

6.4.2 Water

Glutaraldehyde has been detected in waste water originating from hospitals. Measurements of glutaraldehyde concentrations in wastewater from Rouen University Hospital were typically around or below 0.5 mg/L, with the exception of a peak concentration of 3.72 mg/L, which coincided with a weekly disposal of disinfecting solutions (Jolibois et al. 2002).

6.4.3 Sediment and Soil

Monitoring data for glutaraldehyde in soil and sediment were not available.

6.4.4 Other Environmental Media

No information regarding glutaraldehyde concentrations in other environmental media was located.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Primary exposure to glutaraldehyde occurs through inhalation (Smith and Wang 2006), although dermal contact and ingestion may also occur (NIOSH 2000, 2011). Exposure of the general population may be minimal, however, as glutaraldehyde is primarily used in industrial or medical applications (EPA 2007; IPCS 1998). Consumer applications of glutaraldehyde, such as use in cosmetics, are thought to present low concern to the general population. While unlikely, exposure to the general population could occur in health care settings where cleaning agents containing glutaraldehyde are used, primarily in the case of a spill or inadequate rinsing of surfaces; following drift from cooling water towers used in water treatment; from air duct fogging disinfection if proper ventilation procedures are not followed; via household items (i.e., laundry detergents or paints) that use glutaraldehyde as a preservative (e.g., slimicide); or from various sources in the papermaking process (EPA 2007; IPCS 1998). Because glutaraldehyde is used in oil and gas recovery operations (including hydrofracturing processes), there is potential for exposure among workers and among the general population living in areas surrounding such operations. 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. People using masking kits which contain glutaraldehyde for the purpose of defeating potentially positive drug tests may also be exposed to this substance from inhalation or dermal routes (Wu et al. 1994). Patients undergoing selected medical procedures may inadvertently be exposed. For example, glutaraldehyde has been widely implicated as the cause of colitis and diarrhea following endoscopy or sigmoidoscopy procedures, the likely result of contact irritation (e.g., Ahishali et al. 2009; Birnbaum et al. 1995; Dolce et al. 1995; Durante et al. 1992; Fukunaga and Khatibi 2000; Hanson et al. 1998; Rozen et al. 1994; Shih et al. 2011; Stein et al. 2001; West et al. 1995).

Occupational exposure may occur during processes which use or produce glutaraldehyde, particularly when proper ventilation is not used or when products are sprayed (IPCS 1998). This may result from the addition of glutaraldehyde to industrial processes; paper manufacture; aluminum rolling; oil and gas

drilling; x-ray film processing; fogging and spraying for disinfecting purposes; pesticidal applications such as cleaning of animal and poultry cages; and cleaning of medical and dental facilities and equipment (EPA 2007; IPCS 1998).

The primary occupational exposure to glutaraldehyde appears to be inhalation and dermal contact from use in medical and dental applications (EPA 2007; HSDB 2011; IPCS 1998; NICNAS 1994; Smith and Wang 2006). Total exposure depends on the frequency and duration of contact as well as environmental glutaraldehyde concentrations and the use of personal protective equipment (Rietz 1985; Smith and Wang 2006). Medical equipment and dental equipment, such as endoscopes and operating room instruments, are often disinfected using glutaraldehyde solutions at higher concentrations (as high as 2% active ingredient) than used in pesticidal applications (e.g., 0.25% active ingredient for egg sanitation) (EPA 2007). Between 5 and 10% of health care workers are reported to be exposed to glutaraldehyde (Cohen and Patton 2006). Operating room nurses, radiographers, x-ray technicians, and cleaners tend to have the highest health-care related occupational exposure rates (Smith and Wang 2006). Health care workers utilizing cold sterilization procedures and x-ray film processing methods may be exposed to glutaraldehyde concentrations ranging from 0.13 to 2% (HSDB 2011). Air concentrations of glutaraldehyde during disinfection of medical equipment were found to range between <0.5 and 570 ppb, depending on the usage, ventilation, and other conditions. Disinfection via manual methods produced higher air concentrations than automated disinfection processes (EPA 2007). Disinfection of dental equipment using a 2% solution over 5 and 6 minutes resulted in glutaraldehyde air concentrations of 540 and <160 ppb, respectively (EPA 2007). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for glutaraldehyde exposure is 0.05 ppm (Cohen and Patton 2006).

Inhalation is a primary pathway of exposure to personnel in facilities where glutaraldehyde is used or produced. At various glutaraldehyde manufacturing and formulation facilities, glutaraldehyde air concentrations were measured at <10–340 ppb over 15-minute sampling intervals (EPA 2007). Paper manufacturing processes, including application of adhesives, pigments, and fillers, and addition of glutaraldehyde as a slimicide to paper mill process water, can result in exposure. Paper mills using a 50% solution had glutaraldehyde air concentrations ranging from not detectable to 130 ppb over 30–60 minutes (EPA 2007). In a latex plant where a 45% glutaraldehyde solution was used, air concentrations of 27 ppb were observed over a 15-minute time period (EPA 2007).

During aluminum milling processes, air concentrations were found to range from not detectable to 180 ppb (EPA 2007). At a drilling field utilizing a glutaraldehyde-containing product, Aldacide G, air concentrations of 20–120 ppb were measured (EPA 2007).

Glutaraldehyde can be used for spraying and fogging disinfection at poultry houses. Inhalation exposure can occur when personnel enter the facility following application. At various poultry hatcheries and houses, air concentrations of glutaraldehyde ranged from not detectable to 1,060 ppb for 500 and 1,000 ppm solutions with sampling periods ranging from 10 to 60 minutes (EPA 2007). Air concentrations following manual spraying of a 2% solution in a chicken facility, sampled over 15 minutes, ranged from 20 to 120 ppb (EPA 2007). Fogging with a 3% glutaraldehyde solution has also been tested for disinfection following SARS outbreaks (EPA 2007).

Glutaraldehyde exposure may also result from the use of metal working fluids, in cooling tower applications, and during painting processes (EPA 2007). Air concentrations measured while 45% glutaraldehyde-containing metal working fluids were transferred between containers were found to range from <71 to <290 ppb over 16- and 22-minute sample durations, respectively (EPA 2007). Dermal exposure to glutaraldehyde from metalworking fluids could also occur, but is not thought to be a major concern (EPA 2007). Transfer of a 45% solution for a cooling tower application over a 5-minute period resulted in an air concentration of <660 ppb glutaraldehyde (EPA 2007). Around a paint spray booth at an automobile manufacturing plant, a 30-minute sample found air concentrations of glutaraldehyde ranging from not detectable to 158 ppb (EPA 2007).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.8, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Exposure of children to glutaraldehyde is expected to be minimal, as glutaraldehyde is primarily used in industrial and medical applications (EPA 2007; IPCS 1998). It may be possible for children to be exposed to glutaraldehyde residues and vapor in medical facilities, particularly those where improper ventilation exists, or by exposure to paint fumes and household products (i.e., laundry detergent) containing glutaraldehyde (EPA 2007; IPCS 1998). Because glutaraldehyde is used in oil and gas recovery operations (including hydrofracturing processes), there is potential for exposure among children living in areas surrounding such operations. The potential for exposure to glutaraldehyde through ingestion of dust and soil is expected to be low based on the low potential for soil adsorption and the high rate of degradation. Glutaraldehyde has not been detected in breast milk.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The highest glutaraldehyde exposure rates appear to affect personnel working in medical and dental facilities where glutaraldehyde is used as a disinfecting agent (EPA 2007; HSDB 2011; IPCS 1998). Significant exposure may also occur among workers involved in oil and gas recovery operations, although limited information is available regarding exposure levels within such operations.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glutaraldehyde is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of glutaraldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of glutaraldehyde are general well understood and have been discussed in Chapter 4 (Table 4-2). There are no significant data needs.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2011, became available in November of 2012. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Methods of manufacturing and uses of glutaraldehyde are available and have been discussed in Chapter 5. However, import and export volumes were not available. Additional information concerning import and export, release, and disposal of glutaraldehyde is needed.

Environmental Fate. Data suggest that glutaraldehyde is rapidly degradable in air, water, and soil (EPA 2007; HSDB 2011; IPCS 1998; Leung 2001). Additional data do not appear necessary at this time.

Bioavailability from Environmental Media. No data exist regarding glutaraldehyde bioavailability from environmental media such as soil or drinking water. However, glutaraldehyde is known to rapidly biodegrade in soil and water (EPA 2007; Leung 2001); thus, it is not expected to be bioavailable from these sources.

Food Chain Bioaccumulation. Glutaraldehyde is not expected to bioconcentrate due to its ability to be degraded in the environment (HSDB 2011; IPCS 1998). Therefore, bioaccumulation through the food chain is expected to be low (IPCS 1998). No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of glutaraldehyde in contaminated media at hazardous waste sites are needed so that the information obtained on levels of glutaraldehyde in the environment can be used in combination with the known body burden of glutaraldehyde to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Data regarding ambient levels in the environment, particularly near oil and gas recovery operations, would be useful to assess the potential risk to the general population.

Exposure Levels in Humans. Exposure to glutaraldehyde can occur primarily through inhalation and dermal contact with solutions containing glutaraldehyde, such as disinfectants (EPA 2007; IPCS 1998; Smith and Wang 2006). Inhalation and dermal exposures are fairly well understood. However, there is a possibility of exposure through food sources, where animal housing is cleaned with glutaraldehyde solutions. Additional information concerning exposure through ingestion would be useful. Because glutaraldehyde is used in oil and gas recovery operations (including hydrofracturing processes) and pipeline installations, information regarding exposure levels among the workers and among the general population in areas surrounding such operations would be useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children may be exposed to glutaraldehyde through the same routes as adults. However, as occupational settings such as hospitals are the major source of glutaraldehyde exposure, children may not be exposed to detrimental levels of glutaraldehyde. Additional information concerning exposure of children to glutaraldehyde is needed.

Child health data needs relating to susceptibility are discussed in Section 3.13.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for glutaraldehyde were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

No ongoing environmental fate studies for glutaraldehyde were identified using identified in the NIH Research Portfolio Online Reporting Tools (RePORTER 2014).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring glutaraldehyde, its metabolites, and other biomarkers of exposure and effect to glutaraldehyde. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Analytical methods to quantify glutaraldehyde in biological materials are not readily available since the determination of glutaraldehyde in biological matrices is confounded by its reactivity with amine and other functional groups of proteins and enzymes. It is this property that has led to its widespread use as a cross-linking agent for proteins. Furthermore, *in vivo* and *in vitro* studies using laboratory animals suggest that glutaraldehyde is rapidly metabolized in the body. The proposed metabolic pathway of glutaraldehyde has been summarized in Section 3.4.3 (Metabolism) of this profile. Glutaraldehyde can be detected in urine samples by reaction with diethyl thiobarbituric acid in a potassium phosphate buffer solution and measuring the fluorescence of the resultant complex (Wu et al. 1994). This method was discussed in the context of glutaraldehyde's use as a masking agent in which it is added to adulterated urine samples in order to cause false negatives during enzyme immunoassay drug testing rather than as a screening method for exposure to this substance.

Stable-isotope dilution assays involving conventional electron-impact ionization and gas chromatography-mass spectrometry (GS-MS) have been developed to detect and quantify levels of glutaric acid (a metabolite of glutaraldehyde) and other substances in body fluids (Baric et al. 1999; Shigematsu et al. 2005). In the method described by Shigematsu et al. (2005), ethylacetate was used to extract glutaric acid from a mixture containing serum or cerebrospinal fluid, sodium chloride, hydrochloric acid, and known amounts of radiolabeled glutaric acid and 3-hydroxyglutaric acid. Glutaric acid was extracted from urine samples (mixed with creatinine and radiolabeled glutaric acid and 3-hydroxyglutaric acid) by incubation with urease and deproteinization using methanol. The limit of

quantification for glutaric acid in aqueous solution was 0.0019 nmol/mL using QP5050 GC-MS and 0.057 nmol/mL using SSQ710 GC-MS; percent recovery was in the range of 83–86%.

7.2 ENVIRONMENTAL SAMPLES

Atmospheric glutaraldehyde concentrations can be determined by a number of methods. Some methods include thermal desorption/gas chromatographic analysis; OSHA method 64: high performance liquid chromatographic (HPLC) analysis; NIOSH method 2531; silica gel adsorption/gas chromatographic (GC) analysis; alumina adsorption/gas chromatographic analysis; colorimetric determination using 3-methyl-2-benzothiazolinone hydrazone (MBTH); and direct-reading instruments (NICNAS 1994). These methods are summarized in Table 7-1.

In the thermal desorption/GC method, air sampled by a pump is passed through an adsorption tube containing Tenax-GC. The tube is connected to the GC, which is fitted with a flame ionization detector (FID), and the sample is thermally desorbed and separated with temperature programming over approximately 15 minutes (NICNAS 1994).

With the OSHA method 64, samples collected by a pump on 37-mm glass fiber filters are treated with a 5% solution of dinitrophenyl-hydrazine hydrochloride (DNPH), followed by desorption using acetonitrile. The solution is injected into the HPLC, which uses a ultra-violet (UV) absorption detector. For this method, the detection limit has been reported as approximately 0.1 µg and 18 µg/m^3 (HSDB 2011; NICNAS 1994).

A similar HPLC method was also utilized by Sekine et al. (2005) to determine glutaraldehyde concentrations. A passive sampler packed with DNPH was used to collect glutaraldehyde samples in air, eluted with 10 mL of acetonitrile, and concentrations of glutaraldehyde were determined using HPLC. The HPLC utilized a Shimadzu LC-6A pump with an SPD-6A UV-visible detector and the following conditions; a 4.6x150 mm, 5 µm, Inertsil ODS-80A column; a 60/40 acetonitrile/distilled water eluent at 1.5 mL/minute; detection at 360 nm; and an injection volume of 20 µL. The limit of detection was 1.2 ppb of glutaraldehyde for 8-hour sampling (3 times the HPLC baseline noise); the limit of quantitation was 3.9 ppb of glutaraldehyde (10 times the HPLC baseline noise).

Wellons et al. (1998) utilized a method based on OSHA method 64, whereby glutaraldehyde was also measured as a DNPH derivative. A 37 mm filter cassette with DNPH pre-coated AE glass fiber filters

Table 7-1. Analytical Methods for Determining Glutaraldehyde in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing air through sampling tubes containing Amberlite XAD-2 with DNPH	UV spectrophotometer	0.02 mg/m^3 for 3-L air sample		Rietz 1985
Air	Passive sampler containing DNPH; elution with acetonitrile	HPLC	1.2 ppb for 8-hour sample		Sekine et al. 2005
Air	Cassette with DNPH; desorbed with acetonitrile	HPLC with UV detector at 355 nm	0.27 µg/ sample; 0.004 ppm for 15-minute sample		Wellons et al. 1998
Air	Passive badge sampler with DNPH; desorbed with acetonitrile	HPLC with UV detector at 355 nm	0.006 µg/ sample; 0.016 ppm for 15-minute sample		Wellons et al. 1998
Air	Air sampled by pump passed through adsorption tube containing Tenax-GC	GC with FID			NICNAS 1994
Air	Sample on 37 mm glass fiber filter treated with 5% DNPH hydrochloride; desorbed in acetonitrile	HPLC with UV absorption	0.1 µg or 18 µg/m^3		NICNAS 1994
Air	Sample on XAD-2 tube treated with DNPH hydrochloride	GC with FID	0.3 and 1 µg		NICNAS 1994
Air	Samples on adsorption tubes filled with silica gel; desorbed in acetone	GC with FID	0.02 ppm		NICNAS 1994
Air	Samples in adsorption tubes packed with silica gel; desorbed in acetone	GC with FID	0.29 µg/ sample; 0.005 ppm for 15-L sample		Wellons et al. 1998
Air	Samples on adsorption tubes packed with alumina; desorbed with phosphate buffer	GC with Tenax-GC column, FID			NICNAS 1994
Air	Samples drawn through impingers containing distilled water	Colorimetric analysis with MBTH			NICNAS 1994
Air	Direct reading instrument	Fuel cell sensor; glutaraldehyde catalytically oxidized to produce electrical response	0.05–5 ppm v/v or 0.03–4 ppm		NICNAS 1994; Wellons et al. 1998
Air	Diffusive sampler filter with DNPH; washed with acetonitrile	HPLC	0.03 mg/m^3		Lindahl and Levin 1995

Table 7-1. Analytical Methods for Determining Glutaraldehyde in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Diluted 25% glutaraldehyde solutions prepared in methanol	Spectrophotometer with absorbance at 480 nm	1 mg/L		Jolibois et al. 2002
Water	Diluted 25% glutaraldehyde solutions prepared in methanol	GC/MS			Jolibois et al. 2002
Aqueous solutions		Titration with 0.5 N hydroxylamine hydrochloride	10–50% glutaraldehyde solutions		NICNAS 1994
Aqueous solutions	Water sample added to MBTH	Absorbance at 605 or 610 nm	0.5–10 ppm glutaraldehyde solutions		NICNAS 1994
Aqueous solutions	Sodium bisulfide added to water sample	Titrated with standardized sulfuric acid	25–5,000 ppm glutaraldehyde solutions		NICNAS 1994
Aqueous solutions	Water sample	GC with Tenax-GC or Porapak PS column, FID	1–2,500 ppm w/v glutaraldehyde solutions		NICNAS 1994

DNPH = 2,4-dinitrophenylhydrazine; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; MBTH = 3-methyl-2-benzothiazolinone hydrazine; UV = ultraviolet

was used with high-volume personal sample pumps at 1 L/minute to collect 15-minute air samples. The filter cassettes were capped and frozen until analysis, whereby each section was desorbed in 2 mL acetonitrile, with a desorption efficiency of nearly 100%. Solutions were analyzed with HPLC using a UV detector at 355 nm. A lower limit of quantitation of 0.27 µg/sample, or 0.004 ppm for a 15-minute sample was attained, with percent recoveries of 105 and 96% after 17 days ambient temperature and 16 days -20 ºC storage, respectively (Wellons et al. 1998). Similarly, Wellons et al. (1998) also tested a passive badge sampler, containing a filter impregnated with DNPH that has a sampling rate of 5.88 mL/minute. Badges were exposed to air for 15 minutes, then capped. Glutaraldehyde was desorbed with 1 mL acetonitrile and the same HPLC method was utilized. The method was found to have a lower limit of quantification of 0.006 µg/sample, or 0.016 ppm for 15 minutes (Wellons et al. 1998).

The NIOSH method 2531 utilizes a sample collected on washed XAD-2 tubes that are then treated with dinitrophenyl-hydrazine hydrochloride. Samples are analyzed with GC using FID. The detection limit of this method has been reported at both 0.3 and 1 µg (HSDB 2011; NICNAS 1994).

Similarly, Rietz (1985) determined glutaraldehyde concentrations in air by passing known volumes of air through sampling tubes that contained Amberlite XAD-2 that were coated with DNPH as the adsorption material. As the experiment was designed to sample glutaraldehyde as well as formaldehyde and acrolein, acetonitrile was used to elute the resulting hydrazones and the compounds were then separated using an RP C-18 column. The chemicals were identified using a UV spectrophotometer at a wavelength of 365 nm. For a 3-L air sample, the limit of detection for glutaraldehyde was determined to be 0.02 mg/m^3 of air with a 95% confidence level. This method was determined to be acceptable for glutaraldehyde concentrations ranging from 0.04 to 2.1 mg/m^3 of air (Rietz 1985).

A diffusive sampler was used to determine the glutaraldehyde concentrations in air by Lindahl and Levin (1995). The sampler utilized a 20x45 mm filter coated impregnated with DNPH, placed in a 60x30x5-mm polypropylene housing unit along with a 2.9-mm thick screen. The samples were analyzed by eluting the glutaraldehyde-DNPH from the filter with 2.0 or 3.0 mL acetonitrile by shaking for 1 minute and injecting 10 µL samples into the HPLC. The HPLC consisted of two Waters M-6000 A pumps with a Waters M-710 B autosampler and Shimadzu absorbance detector. The detection limit was determined to be approximately 0.03 mg/m^3 for 15-minute samples (Lindahl and Levin 1995).

In the silica gel adsorption/GC analysis method, samples are obtained by a pump on adsorption tubes that are filled with silica gel. The sample is then desorbed with acetone and the solution is injected into a GC

using FID. For 15-minute exposure samples of a 30-L air sample, the detection limit has been reported as 0.02 ppm (NICNAS 1994).

This method of direct measurement of glutaraldehyde in air was evaluated by Wellons et al. (1998). A 70x6 mm (OD) glass tube was packed with silica gel. High-volume personal sample pumps drew air through the tubes at 1 L/minute for 15 minutes. Tubes were then capped and frozen until analysis, where the glutaraldehyde was desorbed with 1 mL of acetone. Glutaraldehyde concentrations were determined by GC using an FID. Losses of 4 and 7% glutaraldehyde occurred from freezing for 14 and 21 days, respectively. A detection limit of 0.29 µg/sample, or 0.005 ppm for a 15-L sample, was attained (Wellons et al. 1998).

Alumina adsorption/GC analysis is accomplished using air samples obtained with a pump. The samples are collected on adsorption tubes packed with alumina. Samples are then desorbed with a phosphate buffer solution and injected into a GC that has a Tenax-GC column and FID installed (NICNAS 1994).

Glutaraldehyde concentrations in air can also be evaluated by colorimetric determination using 3-methyl-2-benzothiazolinone hydrazone (MBTH). Air samples containing are drawn through impingers that contain distilled water, such as with a reciprocating air pump with flow rates up to 1 L/minute. Glutaraldehyde absorbs into the water, due to its soluble nature, and concentrations can then be determined using colorimetric analysis with MBTH solution. This method may be problematic if other aldehydes and ketones are present (NICNAS 1994).

A direct-reading instrument known as the Lion Glutaraldemeter is commercially available for the determination of glutaraldehyde concentrations in air. Air samples of 10 mL are drawn in with a self-contained sample pump, and response times are approximately 60 seconds. A fuel cell sensor in the meter causes glutaraldehyde to go through catalytic oxidation, producing an electrical response, which is proportional to the amount of glutaraldehyde in the air. This method has a reported detection limit of 0.05–5 ppm v/v, although this was also reported as 0.03–4 ppm. The instrument may give erroneous readings if alcohols and other aldehydes are present, although the manufacturer offers an optional filter which removes phenol interference and corrects for alcohol interference (NICNAS 1994; Wellons et al. 1998).

Methods have also been developed to determine glutaraldehyde concentrations in water and aqueous solutions. For high levels of glutaraldehyde in aqueous solutions (i.e., solutions of 10–50%), the standard

method involves titration with 0.5 N hydroxylamine hydrochloride. To determine glutaraldehyde concentrations at lower levels, the following methods may be used: colorimetric determination using MBTH; titration after reaction with sodium bisulfite, and GC analysis. These methods are summarized in Table 7-1.

Colorimetric determination of glutaraldehyde in water is performed by adding the sample to a solution of MBTH and measuring the absorbance at 605 or 610 nm. While the presence of other ketones or aldehydes may interfere, this method is usable for glutaraldehyde concentrations of 0.5–10 ppm in water (NICNAS 1994).

Jolibois et al. (2002) examined glutaraldehyde concentrations in hospital waste water. The study utilized a variation on the spectrophotometric method, whereby standard solutions of a diluted 25% commercial glutaraldehyde solution were prepared in methanol. A coloring reagent mixture of 40 µL of 5% aqueous phenol solution and 10 mL of 70% perchloric acid was prepared. The experiment was performed by adding 100 µL of the methanolic sample to 1 mL of the reagent. After a 15-minute time period for color development, the absorbance was measured on a spectrophotometer at 480 nm. A detection limit of 1 mg/L was obtained. The method was verified by analyzing the methanolic eluates by GC/mass spectrometry (MS) using a Varian 3900 GC with a Saturn 2100 detector, splitless injector (230°C), and CP-SIL 8CB-MS fused silica column (30 m by 0.25 mm ID) with a 1 µL injection volume and helium as the carrier gas (Jolibois et al. 2002).

Glutaraldehyde concentrations in water can also be determined using a titration technique. Sodium bisulfide is added to the water sample to react with the carbonyl groups. The solution is then titrated with standardized sulfuric acid. This method may be used for glutaraldehyde solutions ranging from 25 to 5,000 ppm, but interference by ketones and other aldehydes, as well as acids and bases in the sample, may be an issue (NICNAS 1994).

In GC analysis of glutaraldehyde in water, the sample is injected into a GC equipped with a Tenax-GC or Porapak PS column and a flame ionization detector. This method can detect glutaraldehyde concentrations ranging from 1 to 2,500 ppm w/v (NICNAS 1994).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glutaraldehyde is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of glutaraldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Methods are available to detect glutaric acid (a metabolite of glutaraldehyde) in bodily fluids. Such methods could be applied to detect and quantify glutaraldehyde metabolites in urine and/or serum of glutaraldehyde-exposed workers, although environmental exposure to low levels of glutaraldehyde might not warrant this type of biomonitoring.

Exposure. Additional information concerning procedures to determine glutaraldehyde exposures in biological materials is needed.

Effect. Information concerning procedures to determine the effect of glutaraldehyde in biological materials is needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media.

Methods are available to detect glutaraldehyde in air and water at levels that may be a concern for health. No methods for determining glutaraldehyde concentrations in soil were located, but it is unlikely that this

would be an important environmental medium for glutaraldehyde as it is rapidly degraded in soil, possibly by bacteria.

7.3.2 Ongoing Studies

No ongoing analytical studies for glutaraldehyde were identified in the NIH Research Portfolio Online Reporting Tools (RePORTER 2014).

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of 0.001 ppm ($1x10^{-3}$ ppm) has been derived for acute-duration inhalation exposure (≤14 days) to glutaraldehyde. The MRL is based on a NOAEL of 0.125 ppm and a LOAEL of 0.25 ppm for histopathological nasal lesions in male F344 rats exposed to glutaraldehyde vapor for a single 6-hour period (Gross et al. 1994; NTP 1993). The NOAEL of 0.125 ppm was duration-adjusted to simulate a 24-hour exposure (0.125 ppm x 6 hours/24 hours = $NOAEL_{ADJ}$ of 0.031 ppm) and converted to a HEC ($NOAEL_{HEC}$ = 0.003 ppm) according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract. A total uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for sensitive individuals) was applied.

An MRL of 0.00003 ppm ($3.0x10^{-5}$ ppm) has been derived for intermediate-duration inhalation exposure (15–364 days) to glutaraldehyde. BMD analysis was applied to incidence data for female B6C3F1 mice with inflammation in the nasal vestibule/anterior nares following exposure to glutaraldehyde vapor 6 hours/day, 5 days/week for 13 weeks (NTP 1993). A 10% change from control incidence was selected as the BMR. The resulting 95% lower confidence limit on the maximum likelihood estimate of the exposure concentration associated with the selected BMR ($BMCL_{10}$) of 0.0034 ppm was adjusted to simulate a continuous exposure scenario (0.0034 ppm x 6 hours/24 hours x 5 days/7 days = $BMCL_{10ADJ}$ of 0.0006 ppm). Derivation of a HEC based on the $BMCL_{10ADJ}$ of 0.0006 ppm was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde), resulting in a $BMCL_{10HEC}$ of 0.00008 ppm ($8x10^{-5}$ ppm). A total uncertainty factor of 3 (1 for extrapolation from animals to humans using dosimetric adjustment and 3 for human variability) was applied.

An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to glutaraldehyde. The MRL is based on a NOAEL of 4 mg/kg/day and a LOAEL of 17 mg/kg/day for gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa) in male F344 rats administered glutaraldehyde in the drinking water for 2 years

(van Miller et al. 2002). The NOAEL of 4 mg/kg/day was divided by a total uncertainty factor of 30 (10 for extrapolation from animals to humans and 3 for human variability).

IARC has not classified glutaraldehyde as to its carcinogenicity (IARC 2013). The World Health Organization (WHO) has not established any air quality or drinking water guidelines for glutaraldehyde (WHO 2010, 2011).

OSHA has not established any enforceable standards for glutaraldehyde (OSHA 2013a), although NIOSH and ACGIH have recommended a ceiling limit of 0.2 ppm that should not be exceeded at any time (ACGIH 2013; NIOSH 2011).

The American Industrial Hygiene Association (AIHA) and the Department of Energy (DOE) have established identical values for responding to potential releases of airborne glutaraldehyde for use in community emergency planning. The values established by AIHA (2011) and the DOE (2012) are the Emergency Response Planning Guidelines (ERPGs-1, -2, -3) and Protective Active Criteria (PAC-1, -2, and -3), respectively. These values (0.2, 1, and 5 ppm) represent increasing severity of effects (mild, irreversible, and life-threatening, respectively) for a 1-hour exposure.

EPA and NTP have not classified glutaraldehyde as a carcinogen. The EPA has not derived an oral reference dose (RfD) or an inhalation reference concentration (RfC) for glutaraldehyde (IRIS 2013). ACGIH (2013) has classified glutaraldehyde as an A4 carcinogen (*not classifiable as a human carcinogen*).

Under the Toxic Substances Control Act (TSCA), glutaraldehyde is on the list of chemicals that manufacturers and importers must report for each plant site at which they manufactured or imported glutaraldehyde during the reporting period specified (EPA 2012i, 2012j).

The international and national regulations, advisories, and guidelines regarding glutaraldehyde in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Glutaraldehyde

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV STEL (ceiling)[a]	0.05 ppm	ACGIH 2013
AIHA	ERPG-1[b,c]	0.2 ppm	AIHA 2011
	ERPG-2	1 ppm	
	ERPG-3	5 ppm	
DOE	PAC-1[d]	0.2 ppm	DOE 2012
	PAC-2	1 ppm	
	PAC-3	5 ppm	
EPA	AEGLs	No data	EPA 2013a
	Second AEGL chemical priority list	No data	EPA 2013b
	Hazardous air pollutant	No data	EPA 2013c 42 USC 7412
	NAAQS	No data	EPA 2013f
NIOSH	REL (ceiling TWA)[e]	0.2 ppm	NIOSH 2011
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013a 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013b 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2012a 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012b
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2009c

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Glutaraldehyde

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2012d 40 CFR 117.3
c. Food			
FDA	EAFUS[f]	Yes	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification	A4[g]	ACGIH 2013
EPA	Carcinogenicity classification	No data	IRIS 2013
	RfC	No data	
	RfD	No data	
	Identification and listing of hazardous waste	No data	EPA 2012c 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	Yes	EPA 2013d
	Master Testing List	No data	EPA 2013e
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998e 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2012e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2012f 40 CFR 302.4
	Effective date of toxic chemical release reporting	No data	EPA 2012h 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2012g 40 CFR 355, Appendix A
	TSCA chemical lists and reporting periods		EPA 2012i 40 CFR 712.30
	Effective date	09/30/1991	
	Reporting date	11/27/1991	
	TSCA health and safety data reporting		EPA 2012j 40 CFR 716.120
	Effective date	09/30/1991	
	Reporting date	06/30/1998	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Glutaraldehyde

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2014

[a]Based on upper respiratory tract, skin, and eye irritation and central nervous system impairment. Potential for glutaraldehyde to produce dermal sensitization. The TLV-STEL is a 15-minute TWA exposure that should not be exceeded at any time during an 8-hour workday.
[b]ERPG-1: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor; ERPG-2: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action; ERPG-3: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects (AIHA 2011).
[c]Odor should be detectable near ERPG-1.
[d]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[e]Testing has not been completed to determine the carcinogenicity of glutaraldehyde; however, the limited studies to date indicate that this substance has chemical reactivity and mutagenicity similar to acetaldehyde and malonaldehyde, therefore, NIOSH recommends that careful consideration should be given to reducing exposures to glutaraldehyde (NIOSH 2011).
[f]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[g]A4: not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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9. REFERENCES

*ACGIH. 2013. Glutaraldehyde. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 32.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

*Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Subcommittee on Biomarkers of Organ Damage and Dysfunction. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

*Ahishali E, Uygur-Bayramicli O, Dolapcioglu C, et al. 2009. Chemical colitis due to glutaraldehyde: Case series and review of the literature. Dig Dis Sci 54(12):2541-2545.

*AIHA. 2011. Emergency response planning guidelines (ERPG). Fairfax, VA: American Industrial Hygiene Association. http://www.aiha.org/INSIDEAIHA/GUIDELINEDEVELOPMENT/ERPG/Pages/default.aspx. April 24, 2013.

*Altman PL, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies of Experimental Biology, 1987-2008, 2041.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, and replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

*API. 2015. Hydraulic fracturing. Unlocking America's natural gas resources. American Petroleum Institute. http://www.api.org/~/media/Files/Oil-and-Natural-Gas/Hydraulic-Fracturing-primer/Hydraulic-Fracturing-Primer-2015-highres.pdf. December 9, 2015.

*Arntz D, Fischer A, Hopp M, et al. 2012. Acrolein and methacrolein. In: Ullmann's encyclopedia of industrial chemistry. http://onlinelibrary.wiley.com/doi/10.1002/14356007.a01_149.pub2/abstract. April 6, 2014.

*Azadi S, Klink KJ, Meade BJ. 2004. Divergent immunological responses following glutaraldehyde exposure. Toxicol Appl Pharmacol 197(1):1-8.

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*Cited in text

*Ballantyne B. 1995. Toxicology of glutaraldehyde. Review of studies and human health effects. Dow Chemical. ©The Dow Chemical Company. Do not reproduce without permission.

*Ballantyne B, Jordan SL. 2001. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. J Appl Toxicol 21(2):131-151.

*Ban-Weiss GA, McLaughlin JP, Harley RA, et al. 2008. Carbonyl and nitrogen dioxide emissions from gasoline- and diesel-powered motor vehicles. Environ Sci Technol 42:3944-3950.

*Bardazzi F, Melino M, Alagna G, et al. 1986. Glutaraldehyde dermatitis in nurses. Contact Dermatitis 14(5):319-320.

*Baric I, Wagner L, Feyh P, et al. 1999. Sensitivity and specificity of free and total glutaric acid and 3-hydroxyglutaric acid measurements by stable-isotope dilution assays for the diagnosis of glutaric aciduria type I. J Inherit Metab Dis 22(8):867-881.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*BASF. 2013. [E-mail communication between SRC and BASF and unpublished studies related to Substance: 111-30-8_master_glutaral (IUC4 DSN 559)]. BASF - The Chemical Company. [unpublished study to be peer reviewed].

BASF Corp. 1990a. Report No.: T-2198. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990b. Report No.: T-2203. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990c. Report No.: T-2248. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990d. Report No.: T-2249. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990e. Report No.: T-2287. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

*BASF Corp. 1990f. Report No.: T-2295. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

*BASF Corp. 1990g. Report No.: T-2296. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990h. Report No.: T-2297. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

*BASF Corp. 1990i. Report No.: T-2298. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

*BASF Corp. 1990j. Report No.: T-2299. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

BASF Corp. 1990k. Report No.: T-2303. Letter from BASF Corp to US EPA regarding submission of data on glutaraldehyde with attachments (English and German). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0526410-1.

*BASF Corp. 1990l. Prenatal toxicity range-finding study in rats oral administration (drinking water) (February 02, 1990) (summary tables only) with cover letter dated 121691. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86920000653. OTS0535536.

*BASF Corp. 1990m. Prenatal toxicity range-finding study in rabbits oral administration (gavage) (February 12, 1990) (summary tables only) with cover letter dated 121691. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535535.

*BASF Corp. 1991a. Study of the prenatal toxicity of glutaraldehyde in rabbits after oral administation (gavage) (February 11, 1991) (Final report) with attachment and cover letter dated 121691. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86920000655. OTS0535538.

*BASF Corp. 1991b. Study of the prenatal toxicity of glutaraldehyde in rats after oral administration (drinking water) (February 11, 1991) (Final report) with attachment and cover letter dated 121691. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86920000654. OTS0535537.

*BASF Corp. 1991c. Letter submitting two enclosed prenatal toxicity oral administration range-finding studies (summary tables only) on pentanedial. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86920000656. OTS0535539.

*Beauchamp RO, St Clair MB, Fennell TR, et al. 1992. A critical review of the toxicology of glutaraldehyde. Crit Rev Toxicol 22(3-4):143-174.

*Berger GS, ed. 1994. Epidemiology of endometriosis. In: Endometriosis: Modern surgical management of endometriosis. New York, NY: Springer-Verlag, 3-7.

*Birnbaum BA, Gordon RB, Jacobs JE. 1995. Glutaraldehyde colitis: Radiologic findings. Radiology 195(1):131-134.

9. REFERENCES

*Cain WS, Schmidt R, Jalowayski AA. 2007. Odor and chemesthesis from exposures to glutaraldehyde vapor. Int Arch Occup Environ Health 80(8):721-731.

*Calder IM, Wright LP, Grimstone D. 1992. Glutaraldehyde allergy in endoscopy units. Lancet 339(8790):433.

*Caraccio TR, McGuigan MA. 2004. Formaldehyde and glutaraldehyde. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1246-1250.

*Chan-Yeung M, McMurren T, Catonio-Begley F, et al. 1993. Occupational asthma in a technologist exposed to glutaraldehyde. J Allergy Clin Immunol 91(5):974-978.

*ChemIDplus. 2013. Glutaral. ChemIDplus. Bethesda, MD: U.S. National Library of Medicine. http://sis.nlm.nih.gov/chemical.html. March 20, 2013.

*Chotani GK, Dodge TC, van Scheltinga AHT, et al. 2012. Enzymes, 2. Discovery and production. In: Ullmann's encyclopedia of industrial chemistry. http://onlinelibrary.wiley.com/doi/10.1002/14356007.m09_m01/abstract. April 6, 2014.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Cohen NL, Patton CM. 2006. Worker safety and glutaraldehyde in the gastrointestinal lab environment. Gastroenterol Nurs 29(2):100-104.

*Collins JJ, Burns C, Spencer P, et al. 2006. Respiratory cancer risks among workers with glutaraldehyde exposure. J Occup Environ Med 48(2):199-203.

*Confidential. 1987a. Cytogenicity study-bone marror in-vivo (final report; with attachment, cover sheet and letter dated 112691 (sanitized). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0533792.

*Confidential. 1987b. In vivo alkaline elution assay of WI226.01 for DNA cross links in rat testis with attachments, cover sheet and letter dated 112691 (sanitized). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0533790.

*Confidential. 1987c. In vivo alkaline elution assay of WI226.01 for DNA strand breaks in rat rat testis with attachments, cover sheet and letter dated 112691 (sanitized). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0533791.

Confidential. 1991. Letter to USEPA regarding the enclosed evaluation summary on the lever modification of the Magnusson-Kligman guinea pig maximazation test with glutaraldehyde (sanitized) w-attach. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS05333498.

*Confidential. 2002. 24-Month drinking water study in Wistar rats with glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E/FYI. 8EHQ-0902-15204A. http://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearchView/A93991737DA6857485256D6E0055A03A. April 9, 2014.

*Connaughton P. 1993. Occupational exposure to glutaraldehyde associated with tachycardia and palpitations. Med J Aust 159(8):567.

*Corrado OJ, Osman J, Davies RJ. 1986. Asthma and rhinitis after exposure to glutaraldehyde in endoscopy units. Hum Toxicol 5:325-327.

*Costa LG, Aschner M, Vitalone A, et al. 2004. Developmental neuropathology of environmental agents. Annu Rev Pharmacol Toxicol 44:87-110. 10.1146/annurev.pharmtox.44.101802.121424.

*Cullinan P, Hayes J, Cannon J, et al. 1992. Occupational asthma in radiographers. Lancet 340(Dec):1477.

*Cusano F, Luciano S. 1993. Contact allergy to benzalkonium chloride and glutaraldehyde in a dental nurse. Contact Dermatitis 28(2):127-128.

*Dailey JR, Parnes RE, Aminlari A. 1993. Glutaraldehyde keratopathy. Am J Ophthalmol 115(2):256-258.

*Descotes J. 1988. Identification of contact allergens: The mouse ear sensitization assay. J Toxicol Cutaneous Ocul Toxicol 7(4):263-272.

*Di Prima T, De Pasquale R, Nigro M. 1988. Contact dermatitis from glutaraldehyde. Contact Dermatitis 19(3):219-220.

*Di Stefano F, Siriruttanapruk S, McCoach J, et al. 1999. Glutaraldehyde: An occupational hazard in the hospital setting. Allergy 54(10):1105-1109.

*Dillon D, Combes R, Zeiger E. 1998. The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis 13(1):19-26.

*Di Prima T, De Pasquale R, Nigro M. 1988. Contact dermatitis from glutaraldehyde. Contact Dermatitis 19(3):219-220.

*DOE. 2012. Protective action criteria (PAC). Oak Ridge, TN: U.S. Department of Energy and Subcommittee on Consequence Assessment and Protective Actions (SCAPA). http://orise.orau.gov/emi/scapa/chem-pacs-teels/default.htm. April 24, 2013.

*Dolce P, Gourdeau M, April N, et al. 1995. Outbreak of glutaraldehyde-induced proctocolitis. Am J Infect Control 23(1):34-39.

*Durante L, Zulty JC, Israel E, et al. 1992. Investigation of an outbreak of bloody diarrhea: Association with endoscopic cleaning solution and demonstration of lesions in an animal model. Am J Med 92(5):476-480.

*Ek CJ, Dziegielewska KM, Habgood MD, et al. 2012. Barriers in the developing brain and Neurotoxicology. Neurotoxicology 33(3):586-604. 10.1016/j.neuro.2011.12.009.

*Ema M, Itami T, Kawasaki H. 1992. Teratological assessment of glutaraldehyde in rats by gastric intubation. Toxicol Lett 63(2):147-153.

*Emmanuel E, Hanna K, Bazin C, et al. 2005. Fate of glutaraldehyde in hospital wastewater and combined effects of glutaraldehyde and surfactants on aquatic organisms. Environ Int 31(3):399-406.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development. EPA600890066A. PB90238890.

*EPA. 1991. Guidelines for developmental toxicity risk assessment. U.S. Environmental Protection Agency. EPA600FR91001. http://www2.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf. February 23, 2015.

*EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. U.S. Environmental Protection Agency. EPA600890066F.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

*EPA. 1998a. Health effects test guidelines. OPPTS 870.7800. Immunotoxicity. U.S. Environmental Protection Agency. EPA712C98351. http://www.regulations.gov/contentStreamer?objectId=09000064809bc936&disposition=attachment&contentType=pdf. February 23, 2015.

*EPA. 1998b. Health effects test guidelines. OPPTS 870.6200. Neurotoxicity screening. U.S. Environmental Protection Agency. EPA712C98238. http://www.regulations.gov/contentStreamer?objectId=09000064809bc92e&disposition=attachment&contentType=pdf. February 23, 2015.

*EPA. 1998c. Health effects test guidelines. OPPTS 870.3700. Prenatal developmental toxicity study. U.S. Environmental Protection Agency. EPA712C98207. http://www.regulations.gov/contentStreamer?objectId=09000064809bc488&disposition=attachment&contentType=pdf. February 23, 2015.

*EPA. 1998d. Health effects test guidelines. OPPTS 870.3800. Reproduction and fertility effects. U.S. Environmental Protection Agency. EPA712C98208. http://www.regulations.gov/contentStreamer?objectId=09000064809bc489&disposition=attachment&contentType=pdf. February 23, 2015.

*EPA. 1998e. RCRA waste minimization PBT priority chemical list. U.S. Environmental Protection Agency. Fed Regist 63 FR 60332 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2006. Glutaraldehyde: Report of the cancer assessment review committee. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.

*EPA. 2007. Reregistration eligibility decision for glutaraldehyde. U.S. Environmental Protection Agency. EPA739R07006. http://www.epa.gov/oppsrrd1/REDs/glutaraldehyde-red.pdf. April 5, 2014.

*EPA. 2009a. Drinking water contaminant candidate list. U.S. Environmental Protection Agency. Fed Regist 74 FR 51850:51850-51862. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2009b. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F090004. http://water.epa.gov/drink/contaminants/upload/mcl-2.pdf. April 24, 2013.

*EPA. 2009c. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm. April 24, 2013.

*EPA. 2012a. Designated as hazardous substances in accordance with section 311(b)(2)(a) of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012b. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA 822-S-12-001. http://water.epa.gov/drink/standards/hascience.cfm. April 24, 2013.

*EPA. 2012c. Identification and listing of hazardous waste. Hazardous constituents. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261, Appendix VIII http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012d. Reportable quantities of hazardous substances designated pursuant to section 311 of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 117.3 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012e. Standards for owners and operators of hazardous waste TSD facilities. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 264, Appendix IX http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012f. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.4 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012g. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 355, Appendix A. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012h. Superfund, emergency planning, and community right-to-know programs. Toxic chemical release reporting. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372.65 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012i. Toxic Substances Control Act. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 712.30 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012j. Toxic Substances Control Act. Health and safety data reporting. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 716.120 http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2013a. Acute exposure guideline levels (AEGLs). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/oppt/aegl/. April 24, 2013.

*EPA. 2013b. Acute exposure guideline levels (AEGLs). Second AEGL chemical priority list. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/aegl/pubs/priority_2.htm. April 24, 2013.

*EPA. 2013c. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code 42 USC 7412 http://www.epa.gov/ttn/atw/orig189.html. April 24, 2013.

*EPA. 2013d. Inert ingredients permitted for use in nonfood pesticide products. Washington, DC: U.S. Environmental Protection Agency. http://iaspub.epa.gov/apex/pesticides/f?p=124:1. April 24, 2013.

*EPA. 2013e. Master testing list. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/chemtest/pubs/mtl.html. April 24, 2013.

*EPA. 2013f. National ambient air quality standards (NAAQS). Washington, DC: Office of Air and Radiation, U.S. Environmental Protection Agency. http://www.epa.gov/air/criteria.html. April 24, 2013.

*EPA. 2013g. Gludaraldehyde. Inert finder. U.S. Environmental Protection Agency. http://iaspub.epa.gov/apex/pesticides/f?p=INERTFINDER:3:0::NO::P3_ID:7419. March 20, 2013.

*FDA. 2007. Redbook 2000. Guidance for industry and other stakeholders toxicological principles for the safety assessment of food ingredients U.S. Food and Drug Administration. http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf. February 23, 2015.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. April 24, 2013.

*Fomon SJ. 1966. Body composition of the infant: Part 1: The male reference infant. In: Faulkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35(Suppl 5):1169-1175.

*Fowler JF. 1989. Allergic contact dermatitis from glutaraldehyde exposure. J Occup Med 31(10):852-853.

*Frantz SW, Beskitt JL, Tallant MJ, et al. 1993. Glutaraldehyde: Species comparisons of in vitro skin penetration. J Toxicol Cutaneous Ocul Toxicol 12(4):349-361.

*Fukunaga K, Khatibi A. 2000. Glutaraldehyde colitis: A complication of screening flexible sigmoidoscopy in the primary care setting. Ann Intern Med 133(4):315.

*Galloway SM, Bloom AD, Resnick M, et al. 1985. Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ Mutagen 7:1-51.

*Gannon PF, Bright P, Campbell M, et al. 1995. Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments. Thorax 50(2):156-159.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(Supp 2):65-71.

*Greenberg MI. 2002. Healthcare worikers. In: Goldfrank LR, Howland MA, Flomenbaum NE, et al., eds. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill Medical Publishing Division, 1677-1678.

*Gross EA, Mellick PW, Kari FW, et al. 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(3):348-362.

*Guthua SW, Macigo FG, Mwaniki DL, et al. 2001. Symptoms in health personnel exposed to disinfectants. East Afr Med J 78(3):157-160.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.

*Halatek T, Opalska B, Swiercz R, et al. 2003. Glutaraldehyde inhalation exposure of rats: effects on lung morphology, Clara-cell protein, and hyaluronic acid levels in BAL. Inhal Toxicol 15(1):85-97.

*Hamann CP, Rodgers PA, Sullivan K. 2003. Allergic contact dermatitis in dental professionals: effective diagnosis and treatment. J Am Dent Assoc 134(2):185-194.

*Hansen KS. 1983a. Glutaraldehyde occupational dermatitis. Contact Dermatitis 9(1):81-82.

*Hansen KS. 1983b. Occupational dermatoses in hospital cleaning women. Contact Dermatitis 9(5):343-351.

*Hanson JM, Plusa SM, Bennett MK, et al. 1998. Glutaraldehyde as a possible cause of diarrhoea after sigmoidoscopy. Br J Surg 85(10):1385-1387.

*Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5(Suppl 1):3-142.

*HazDat. 2007. Glutaraldehyde. HazDat Database: ATSDR’s Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

*Hemminki K, Falck K, Vainio H. 1980. Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals. Arch Toxicol 46:277-285.

*Hemminki K, Kyyronen P, Lindbohm ML. 1985. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Community Health 39(2):141-147.

*Hemminki K, Mutanen P, Saloniemi I, et al. 1982. Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. Br Med J (Clin Res Ed) 285(6353):1461-1463.

*Hilton J, Dearman RJ, Harvey P, et al. 1998. Estimation of relative skin sensitizing potency using the local lymph node assay: A comparison of formaldehyde with glutaraldehyde. Am J Contact Dermat 9(1):29-33.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Hoechst Celanese Corp. 1981. An acute inhalation toxicity study of C-204 in the rat with glutaraldehyde (project report) with cover letter dated 112791. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86-920000304. OTS0533523.

*HSDB. 2011. Glutaraldehyde. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. April 6, 2014.

*IARC. 2013. Agents classified by the IARC monographs. Volumes 1-107. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/index.php. April 24, 2013.

*IPCS. 1998. Glutaradehyde. OECD Screening informtaion dataset (SIDS) high production volume chemicals. International Programme on Chemical Safety. http://www.inchem.org/documents/sids/sids/111308.pdf. April 5, 2014.

*IPCS. 2000. Glutaradehyde. International Chemical Safety Cards (ICSCs). International Programme on Chemical Safety. http://www.inchem.org/documents/icsc/icsc/eics0158.htm. March 20, 2013.

*IRIS. 2013. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/. April 24, 2013.

*Jachuck SJ, Bound CL, Steel J, et al. 1989. Occupational hazard in hospital staff exposed to 2 per cent glutaraldehyde in an endoscopy unit. J Soc Occup Med 39(2):69-71.

*Jolibois B, Guerbet M, Vassal S. 2002. Glutaraldehyde in hospital wastewater. Arch Environ Contam Toxicol 42(2):137-144.

*Jordan WJ, Dahl MV, Albert HL. 1972. Contact dermatitis from gluraldehyde. Arch Dermatol 105(1):94-95.

*Jung R, Engelhart G, Herbolt B, et al. 1992. Collaborative study of mutagenicity with Salmonella typhimurium TA102. Mutat Res 278:265-270.

*Kamber M, Flückiger-Isler S, Engelhardt G, et al. 2009. Comparison of the Ames II and traditional Ames test responses with respect to mutagenicity, strain specificities, need for metabolism and correlation with rodent carcinogenicity. Mutagenesis 24(4):359-366.

*Kanerva L, Miettinen P, Alanko K, et al. 2000. Occupational allergic contact dermatitis from glyoxal, glutaraldehyde and neomycin sulfate in a dental nurse. Contact Dermatitis 42(2):116-117.

*Katagiri H, Yamamoto T, Uchimura A, et al. 2011. The alterations in neurotransmitters and their metabolites in discrete brain regions in the rats after inhalation of disinfectant, glutaraldehyde or ortho-phthalaldehyde for 4 weeks. Ind Health 49(3):328-337.

9. REFERENCES

*Kearns GL, Abdel-Rahman SM, Alander SW, et al. 2003. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157-1167. 10.1056/NEJMra035092.

*Kiec-Swierczynska M, Krecisz B. 2001. Occupational allergic contact dermatitis in hairdressers due to glutaraldehyde. Contact Dermatitis 44(3):185-186.

*Kieć-Świerczyńska M, Krecisz B, Pałczyński C, et al. 2001. Allergic contact dermatitis from disinfectants in farmers. Contact Dermatitis 45(3):168-169.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29(18):4430-4433.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kucenic MJ, Belsito DV. 2002. Occupational allergic contact dermatitis is more prevalent than irritant contact dermatitis: A 5-year study. J Am Acad Dermatol 46(5):695-699.

*Kuchenmeister F, Schmezer P, Engelhardt G. 1998. Genotoxic bifunctional aldehydes produce specific images in the comet assay. Mutat Res 419:69-78.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*Leikin JB, Paloucek FP. 2002. Glutaraldehyde. In: Poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 625-626.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Leung HW. 2001. Aerobic and anaerobic metabolism of glutaraldehyde in a river water-sediment system. Arch Environ Contam Toxicol 41(3):267-273.

*Levin DE, Hollstein M, Christman MF, et al. 1982. A new Salmonella tester strain (TA102) with A-T base pairs at the site of mutation detects oxidative mutagens. Proc Natl Acad Sci USA 79:7445-7449.

*Lewis RJ. 2007. Glutaraldehyde. In: Hawley's condensed chemical dictonary. 15th ed. Hoboken, NJ: John Wiley & Sons, Inc., 610.

*Lindahl R, Levin JO. 1995. Laboratory validation of a diffusive sampler for the determination of glutaraldehyde in air. J Chromatogr A 710(1):175-180.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

*Maibach H. 1975. Glutaraldehyde: Cross-reactions to formaldehyde? Contact Dermatitis 1(5):326-327.

*Marnett LJ, Hurd HK, Hollstein MC, et al. 1985. Naturally occurring carbonyl compounds are mutagens in Salmonella tester strain TA104. Mutat Res 148:25-34.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

*McCurdy R. 2011. EPA hydraulic fracturing workshop 1. February 24-25, 2011. Chesapeake Energy. http://www.epa.gov/sites/production/files/documents/highratehfinnon-marcellusunconventionalshale.pdf. December 9, 2015.

*McEntee T. 2000. Industrial antimicrobial agents. In: Kirk-Othmer encyclopedia of chemical technology. http://onlinelibrary.wiley.com/doi/10.1002/0471238961.0914042113030514.a01/abstract. April 6, 2014.

*McGinley HR. 2012. Glutarldehyde uses and counterfeits. Water Technol 35(9):30-33.

*McGregor DB, Brown A, Cattanach P, et al. 1988. Responses of the L5178Y tk-positive/tk-negative mouse lymphoma cell forward mutation assay II: 18 coded chemicals. Environ Mol Mutagen 11(1):91-118.

*Mckelvey JA, Garman RH, Anuszkiewicz CM, et al. 1992. Percutaneous pharmacokinetics and material balance studies with glutaraldehyde. Cutan Ocul Toxicol 11(4):341-367.

*Mirsalis JC, Tyson CK, Steinmetz KL, et al. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: Testing of 24 compounds. Environ Mol Mutagen 14(3):155-164.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5(6):485-527.

*Myers DR, Pashley DH, Lake FT, et al. 1986. Systemic absorption of 14C-glutaraldehyde from glutaraldehyde-treated pulpotomy sites. Pediatr Dent 8(3):134-138.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

*Neeper-Bradley TL, Ballantyne B. 2000. Two-generation reproduction study by dosing with glutaraldehyde in the drinking water of CD rats. J Toxicol Environ Health A 60:107-129.

*Nethercott JR, Holness DL, Page E. 1988. Occupational contact dermatitis due to glutaraldehyde in health care workers. Contact Dermatitis 18(4):193-196.

*Nettis E, Colanardi MC, Soccio AL, et al. 2002. Occupational irritant and allergic contact dermatitis among healthcare workers. Contact Dermatitis 46:101-107.

*NICNAS. 1994. Priority existing chemical Number 3. Glutaraldehyde. Full public report. Canberra, Australia: National Industerial Chemicals Notification and Assessment Scheme. Australian Government Publishing Service.

*NIOSH. 1987a. Glutaraldehyde at Montgomery Hospital, Norristown, Pennsylvania Health Hazard Evaluation (HHE). Cincinnati, OH: National Institute for Occupational Safety and Health. HETA862261769. http://www.cdc.gov/niosh/hhe/reports/pdfs/1986-0226-1769.pdf. April 10, 2014.

*NIOSH. 1987b. Health Hazard Evaluation Report HETA 85-257-1791, Mercy Medical Center, Denver, Colorado. Cincinnati, OH: National Institute for Occupational Safety and Health. HETA852571791.

*NIOSH. 2000. Gludaraldehyde. International Chemical Safety Cards. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/ipcsneng/neng0158.html. April 6, 2014

*NIOSH. 2011. Glutaraldehyde. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0301.html. April 6, 2014.

*Norbäck D. 1988. Skin and respiratory symptoms from exposure to alkaline glutaraldehyde in medical services. Scand J Work Environ Health 14(6):366-371.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council. National Academy Press. PB93216091.

*NTP. 1993. NTP Technical report on toxicity studies of glutaraldehyde (CAS No. 111-30-8) administered by inhalation to F344/N rats and B6C3F1 mice. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. NIH Publication 93-3348, Number 25.

*NTP. 1999. NTP Technical Report on the toxicology and carcinogenesis studies of glutaraldehyde in F344/N rats and B6C3F1 mice. Inhalation studies. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. NIH Publication No. 99-3980. NTP TR490.

*NTP. 2013a. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments—February 2013. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. October 15, 2014.

*NTP. 2013b. Appendix 2: Guidance for assessing risk of bias in the protocol for evaluating the evidence for an association between pfoa and pfos exposure and immunotoxicity. In: Systematic review to evaluate the evidence for an association between perfluorooctanoic acid (PFOA) or perflurooctane sulfonate (PFOS) exposure and immunotoxicity. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/appendix_2_pfoa_pfos_riskofbias.pdf. February 26, 2015.

*NTP. 2014. Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf. November 30, 2015.

*Nunoshiba T, Hashimoto M, Nishioka H. 1991. Cross-adaptive response in Escherichia coli caused by pretreatment with H2O2 against formaldehyde and other aldehyde compounds. Mutat Res 255(3):265-271.

*OECD. 1983. Test No. 415: One-generation reproduction toxicity study. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-415-one-generation-reproduction-toxicity-study_9789264070844-en. February 23, 2015.

*OECD. 1992. Test No. 406: Skin sensitisation. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-406-skin-sensitisation_9789264070660-en. February 23, 2015.

*OECD. 1998. Test No. 408: Repeated dose 90-day oral toxicity study in rodents. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en. February 23, 2015.

*OECD. 2001a. Test No. 414: Prenatal development toxicity study. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820-en. February 23, 2015.

*OECD. 2001b. Test No. 416: Two-generation reproduction toxicity. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-416-two-generation-reproduction-toxicity_9789264070868-en. February 23, 2015.

*OECD. 2009a. Test No. 412: Subacute inhalation toxicity: 28-Day study. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-412-subacute-inhalation-toxicity-28-day-study_9789264070783-en. February 23, 2015.

*OECD. 2009b. Test No. 451: Carcinogenicity studies. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-451-carcinogenicity-studies_9789264071186-en. February 23, 2015.

*OECD. 2009c. Test No. 452: Chronic toxicity studies. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-452-chronic-toxicity-studies_9789264071209-en. February 23, 2015.

*OECD. 2009d. Test No. 453: Combined chronic toxicity/carcinogenicity studies. OECD guidelines for the testing of chemicals, section 4: Health effects. OECD ilibrary. Organisation for Economic Co-operation and Development. http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies_9789264071223-en. February 23, 2015.

*Ong TH, Tan KL, Lee HS, et al. 2004. A case report of occupational asthma due to glutaraldehyde exposure. Ann Acad Med Singapore 33(2):275-278.

*OSHA. 2013a. Toxic and hazardous substances. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 1910.1000, Table Z-1. http://www.osha.gov/law-regs.html. April 24, 2013.

*OSHA. 2013b. List of highly hazardous chemicals, toxics, and reactives. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 1910.119, Appendix A. http://www.osha.gov/law-regs.html. April 24, 2013.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Palczynski C, Walusiak J, Krakowiak A, et al. 2005. Glutaraldehyde-induced occupational asthma: BALF components and BALF and serum Clara cell protein (CC16) changes due to specific inhalatory provocation test. Occup Med (Lond) 55(7):572-574.

*Palczynski C, Walusiak J, Ruta U, et al. 2001. Occupational asthma and rhinitis due to glutaraldehyde: Changes in nasal lavage fluid after specific inhalatory challenge test. Allergy 56(12):1186-1191.

*Perera PM, Kularathne K, Gawarammana IB. 2008. Laryngeal edema and metabolic acidosis after Omnicide ingestion. Clin Toxicol (Phila) 46(9):858-860.

*Peters K, Richards FM. 1977. Chemical cross-linking: Reagents and problems in studies of membrane structure. Annu Rev Biochem 46:523-551.

*Pisaniello DL, Gun RT, Tkaczuk MN, et al. 1997. Glutaraldehyde exposures and symptoms among endoscopy nurses in South Australia. Appl Occup Environ Hyg 12(3):171-177.

*Potter DW, Wederbrand KS. 1995. Total IgE antibody production in BALB/c mice after dermal exposure to chemicals. Fundam Appl Toxicol 26(1):127-135.

*Quirce S, Gomez M, Bombin C, et al. 1999. Glutaraldehyde-induced asthma. Allergy 54(10):1121-1122.

*Ranly DM, Horn D. 1990. Distribution, metabolism, and excretion of [14C] glutaraldehyde. J Endod 16(3):135-139.

*Ranly DM, Amstutz L, Horn D. 1990. Subcellular localization of glutaraldehyde. Endod Dent Traumatol 6(6):251-254.

*Ravis SM, Shaffer MP, Shaffer CL, et al. 2003. Glutaraldehyde-induced and formaldehyde-induced allergic contact dermatitis among dental hygienists and assistants. J Am Dent Assoc 134(8):1072-1078.

*Reifenrath WG, Prystowsky SD, Nonomura JH, et al. 1985. Topical glutaraldehyde-percutaneous penetration and skin irritation. Arch Dermatol Res 277(3):242-244.

*RePORTER. 2014. Glutaraldehyde. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. April 7, 2014.

*Rietz B. 1985. Determination of three aldehydes in the air of working environments. Anal Lett 18(19):2369-2379.

*Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. 10.1289/ehp.1307972.

*Rozen P, Somjen GJ, Baratz M, et al. 1994. Endoscope-induced colitis: Description, probable cause by glutaraldehyde, and prevention. Gastrointest Endosc 40(5):547-553.

*Ruiz-Rubion M, Alejandre-Duran E, Pueyo C. 1985. Oxidative mutagens specific for A-T base pairs induce forward mutations to L-arabinose resistance in Salmonella typhimurium. Mutat Res 147:153-163.

*Sakagami Y, Yamazaki H, Ogasawara N, et al. 1988b. The evaluation of genotoxic activities of disinfectants and their metabolites by umu test. Mutat Res 209:155-160.

*Sakagami Y, Yamasaki K, Yokoyama H, et al. 1988a. DNA repair test of disinfectants by liquid rec-assay. Mutat Res 193(1):21-30.

*Sanderson KV, Cronin E. 1968. Glutaraldehyde and contact dermatitis. Br Med J 3(5621):802.

*Sano LL, Krueger AM, Landrum PF. 2005. Chronic toxicity of glutaraldehyde: Differential sensitivity of three freshwater organisms. Aquat Toxicol 71(3):283-296.

*Sasaki Y, Endo R. 1978. Mutagenicity of aldehydes in Salmonella. Mutat Res 54(2):251-252.

*Saunders NR, Ek CJ, Habgood MD, et al. 2008. Barriers in the brain: A renaissance? Trends Neurosci 31(6):279-286. 10.1016/j.tins.2008.03.003.

*Saunders NR, Liddelow SA, Dziegielewska KM. 2012. Barrier mechanisms in the developing brain. Frontiers in pharmacology 3:Article 46. 10.3389/fphar.2012.00046.

*Scheuplein R, Charnley G, Dourson M. 2002. Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35(3):429-447.

*Sekine Y, Oikawa D, Saitoh K, et al. 2005. Evaluation of passive sampler for measurement of glutaraldehyde in occupational indoor air. J Health Sci 51(6):629-635.

*Shaffer MP, Belsito DV. 2000. Allergic contact dermatitis from glutaraldehyde in health-care workers. Contact Dermatitis 43(3):150-156.

*Shigematsu Y, Hata I, Tanaka Y, et al. 2005. Stable-isotope dilution gas chromatography-mass spectrometric measurement of 3-hydroxyglutaric acid, glutaric acid and related metabolites in body fluids of patients with glutaric aciduria type 1 found in newborn screening. J Chromatogr B Analyt Technol Biomed Life Sci 823(1):7-12.

*Shih HY, Wu DC, Huang WT, et al. 2011. Glutaraldehyde-induced colitis: Case reports and literature review. Kaohsiung J Med Sci 27(12):577-580.

*Siebert J, Harke HP. 2012. Disinfectants. In: Ullmann's encyclopedia of industrial chemistry. http://onlinelibrary.wiley.com/doi/10.1002/14356007.a08_551.pub2/abstract. April 6, 2014.

*Simonenko V, Syuch N, Prostakishin G, et al. 2009. Unfavorable outcome in severe systemic toxicity after concentrated glutaraldehyde ingestion. Toxicology Letters (Shannon) 189(Sp. Iss. SI):S253.

*Slesinski RS, Hengler WC, Guzzie PJ, et al. 1983. Mutagenicity evaluation of glutaraldehyde in a battery of in vitro bacterial and mammalian test systems. Food Chem Toxicol 21(5):621-629.

*Smith DR, Wang R. 2006. Glutaraldehyde exposure and its occupational impact in the health care environment. Environ Health Prev Med 11:3-10.

*Speit G, Neuss S, Schutz P, et al. 2008. The genotoxic potential of glutaraldehyde in mammalian cells in vitro in comparison with formaldehyde. Mutat Res 649(1-2):146-154.

*St Clair MB, Bermudez E, Gross EA, et al. 1991. Evaluation of the genotoxic potential of glutaraldehyde. Environ Mol Mutagen 18(2):113-119.

*Stein BL, Lamoureux E, Miller M, et al. 2001. Glutaraldehyde-induced colitis. Can J Surg 44(2):113-116.

*Stern ML, Holsapple MP, Ja, et al. 1989. Contact hypersensitivity response to glutaraldehyde in Guinea pigs and mice. Toxicol Ind Health 5(1):31-43.

*Stingeni L, Lapomarda V, Lisi P. 1995. Occupational hand dermatitis in hospital environments. Contact Dermatitis 33(3):172-176.

*Stromberg PC, Vogtsberger LM, Marsh LR, et al. 1983. Pathology of the mononuclear cell leukemia of Fischer rats. II. Hematology. Vet Pathol 20:709-717.

*Tam M, Freeman S. 1989. Occupational allergic contact dermatitis due to glutaraldehyde: a study of six cases due to Wavicide and Aldecyde. J Occup Health Safety—Aust NZ 5:487-491.

*Teta MJ, Avashia BH, Cawley TJ, et al. 1995. Absences of sensitizations and cancer increases among glutaraldehyde workers. Toxic Subst Mech 14:293-305.

*Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

*Thomas S, Russell AD. 1974. Temperature-induced changes in the sporicidal activity and chemical properties of glutaraldehyde. Appl Microbiol 28(3):331-335.

*Trigg C, Heap D, Herdman M, et al. 1992. A radiographer's asthma. Respir Med 86(2):167-169.

*Tsai CC, Huang RN, Sung HW, et al. 2000. In vitro evaluation of the genotoxicity of a naturally occurring crosslinking agent (genipin) for biologic tissue fixation. J Biomed Mater Res 52(1):58-65.

*Uhr H, Mielke B, Exner O, et al. 2013. Biocides. In: Ullmann's encyclopedia of industrial chemistry. http://onlinelibrary.wiley.com/doi/10.1002/14356007.a16_563.pub2/abstract. April 9, 2014.

*Unal M, Yucel I, Akar Y, et al. 2006. Outbreak of toxic anterior segment syndrome associated with glutaraldehyde after cataract surgery. J Cataract Refract Surg 32(10):1696-1701.

Union Carbide. 1991. Letter submitting multiple enclosed studies on multiple chemicals with attachment. Union Carbide Chemicals and Plastics Company Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991a. Report 17-61. Range finding tests on glutaraldehyde (25% aqueous). Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991b. Report 24-80. Progress report for the month ended August 31, 1961. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991c. Special report 37-54. Miscellaneous toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991d. Special report 38-111. Glutaraldehyde. Results of feeding in the diets of rats for 7 days. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991e. Special report 38-146. UCARCIDE sanitizer 401 and 402 (sanitizer 402 is one part sanitizer 401; 9 parts water) range finding toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991f. Report 39-5. Glutaraldehyde. Results of inclusion in the drinking water of rats for 4 days. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991g. Special report 39-40. Miscellaneous toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991h. Project report 41-77. Miscellaneous toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991i. Project report 44-7. UCARCIDE antimicrobial 125LT. D.O.T. skin irritation study. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991j. Project report 44-15. UCARCIDE 250 antimicrobial. Department of Transportation (D.O.T.) skin corrosivity tests. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991k. Project report 44-65. Glutaraldehyde dilutions. Percutaneous toxicity and eye irritation studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991l. Project report 45-124. Glutaraldehyde dilutions. Acute peroral toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991m. Project report 47-33. Glutaraldehyde dilutions. Primary skin and eye irritancy studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991n. Project report 47-166. Aqucar 514 water treatment microbiocide. Acute toxicity and irritancy study. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991o. Project report 47-190. Glutaraldehyde. Two-week inclusion in drinking water of rats. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991p. Project report 48-3. Aqucar 514. Acute inhalation toxicity study. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991q. Project report 48-51. Glutaraldehyde dilutions (45%, 15% and 10%). Acute percutaneous studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991r. Project report 48-107. Addendum to glutaraldehyde: Ninety-day inclusion in drinking water. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991s. Project report 49-97. UCARCIDE instrument sterilant 602. Acute peroral toxicity study in the rat. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991t. Project report 50-92. UCARCIDE 145LT. Acute peroral toxicity study in the rat. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991u. Report 50-105. UCARCIDE antimicrobial 145LT. Acute percutaneous and inhalation toxicity studies. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991v. Laboratory project ID 51-27. Glutaradehyde: Fourteen-day drinking water toxicity study in mice. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991w. Laboratory project ID 52-1. Glutaraldehyde: Ninety-day drinking water toxicity study in mice. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991x. Laboratory project ID 53-8. UCARCIDE antimicrobial 250. Acute vapor inhalation toxicity test in rats. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991y. Project report 44-107. Evaluation of subchronic dermal toxicity of glutaraldehyde in mice. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991z. Laboratory project ID 50-101. UCARCIDE antimicrobial 145LT. Acute peroral toxicity study in the rat. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991aa. Laboratory project ID 50-102. UCARCIDE antimicrobial 145LT. Acute percutaneous toxicity study in the rabbit. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

Union Carbide Chem & Plas Co. 1991bb. Laboratory project ID 50-103. UCARCIDE antimicrobial 145LT primary skin irritancy study in the rabbit. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991cc. Laboratory project ID 50-104. UCARCIDE antimicrobial 145LT primary eye irritancy study in the rabbit. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991dd. Project report 52-10. Glutaraldehyde: 2-Week dosing feasibility study in dogs with administration via the drinking water or by gavage. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991ee. Project report 52-93. Glutaraldehyde: 13-Week toxicity study in dogs with administration via the drinking water. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991ff. Project report 43-130. A preliminary material balance study of glutaraldehyde in the rats. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991gg. Project report 43-16. Glutaraldehyde (50%). In vitro mutagenesis studies: 3-Test battery. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991hh. Project report 44-67. Glutaraldehyde (50%). In vitro mutagenesis studies: CHO mutation test. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991ii. Project report 44-131. Glutaraldehyde. Salmonella/microsome (Ames). Bacterial mutagenicity assay. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1991jj. Laboratory project ID 54-101. UCARCIDE antimicrobial 250 (Glutaraldehyde, 50% aqueous solution): In vitro chromosomal aberrations assay in Chinese hamster ovary cells. Letter submitting multiple enclosed studies on multiple chemicals with attachments. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535072.

*Union Carbide Chem & Plas Co. 1992. UCARCIDE antimicrobial 250: Acute peroral toxicity study in the rat (final report) with cover letter dated 011692. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86920000753. OTS0535081.

*Union Carbide Corp. 1966. Repeated insult patch test of glutaraldehyde, 5% solution, with cover letter dated 11/14/95. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0558276.

*Union Carbide Corp. 1976. Human sensory irritation threshold of glutaraldehyde vapor, with cover letter dated 4/11/96. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86960000358. OTS0558406.

*Union Carbide Corp. 1980. Repeated insult patch test of glutaraldehyde (0.1%, 0.2%, 0.5% solution) with cover letter dated 11/14/95. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86960000134. OTS0558274.

Union Carbide Corp. 1991. Letter submitting an occular and respiratory irritation study for two glutaraldehye containing aqueous mixtures. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86-930000216. OTS0537659.

*Union Carbide Corp. 1992a. Report 27-137. Range finding tests on glutaraldehyde, 45% aqueous. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992b. Project report 40-50. Glutaraldehye, 50% aqueous solution. Range finding toxicity studies. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992c. Project report 40-120. Glutaraldehyde 25% aqueous. Range finding toxicity studies. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992d. Project report 46-63. Glutaraldehyde vapor nine-day inhalation study on rats. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992e. Project report 46-95. Glutaraldehyde vapor nine-day inhalation study on rats. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992f. Project report 46-101. Glutaraldehyde vapor subchronic inhalation study on rats. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

Union Carbide Corp. 1992g. Project report 47-21. Glutaraldehyde. Acute inhalation toxicity with chamber analysis. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP.

*Union Carbide Corp. 1992h. Project report 51-14. 50% Aqueous glutaraldehyde samples (UGARCID 250 and BASF 50% glutaraldehyde. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992i. Project report 51-37. Glutaraldehye dilutions: Acute peroral toxicity studies in the mouse. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992j. Project report 52-116. 50% Glutaraldehye (UCARCIDE 250) primary skin irritancy studies in the rabbit. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

Union Carbide Corp. 1992k. Project report 44-97. Glutaraldehyde. Six-hour static LT50 on rats. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

*Union Carbide Corp. 1992l. Report 44-96. Glutaraldehyde four-hour LC50 inhalation study on rats. Initial submission: Letter submitting twelve enclosed toxicology studies on glutaraldehyde. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. OTS0536179.

Union Carbide Corp. 1996. Human sensory irritation threshold of glutaraldehyde vapor, with cover letter dated 04/11/1996. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0558406.

*U.S. Coast Guard. 2004. Evaluation of biocides for potential treatment of ballast water. Washington, DC: United States Coast Guard. ADA429663.

*van Birgelen AP, Chou BJ, Renne RA, et al. 2000. Effects of glutaraldehyde in a 2-year inhalation study in rats and mice. Toxicol Sci 55(1):195-205.

*van Miller JP, Hermansky SJ, Losco PE, et al. 2002. Chronic toxicity and oncogenicity study with glutaraldehyde dosed in the drinking water of Fischer 344 rats. Toxicology 175(1-3):177-189.

*van Triel JJ, van Bree BW, Roberts DW, et al. 2011. The respiratory allergen glutaraldehyde in the local lymph node assay: Sensitization by skin exposure, but not by inhalation. Toxicology 279(1-3):115-122.

*Varpela E, Otterstrom S, Hackman R. 1971. Liberation of alkalinized glutaraldehyde by respirators after cold sterilization. Acta Anaesthesiol Scand 15(4):291-298.

*Vergnes JS, Ballantyne B. 2002. Genetic toxicology studies with glutaraldehyde. J Appl Toxicol 22(1):45-60.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483.

*Vock EH, Lutz WK, Ilinskaya O, et al. 1999. Discrimination between genotoxicity and cytotoxicity for the induction of DNA double-strand breaks in cells treated with aldehydes and diepoxides. Mutat Res 441(1):85-93.

*von der Hude W, Behm C, Gurtler R, et al. 1988. Evaluation of the SOS chromotest. Mutat Res 203:81-94.

*Vyas A, Pickering CA, Oldham LA, et al. 2000. Survey of symptoms, respiratory function, and immunology and their relation to glutaraldehyde and other occupational exposures among endoscopy nursing staff. Occup Environ Med 57(11):752-759.

*Waldron HA. 1992. Glutaraldehyde allergy in hospital workers. Lancet 339(8797):880.

*Watanabe K, Sakamoto K, Sasaki T. 1998. Comparisons on chemically-induced mutation among four bacterial strains, Salmonella typhimurium TA102 and TA2638, and Escherichia coli WP2/pKM101 and WP2 uvrA/pKM101. Mutat Res 412:17-31.

*Waters A, Beach J, Abramson M. 2003. Symptoms and lung function in health care personnel exposed to glutaraldehyde. Am J Ind Med 43(2):196-203.

*Wellons SL, Trawick EG, Stowers MF, et al. 1998. Laboratory and hospital evaluation of four personal monitoring methods for glutaraldehyde in ambient air. Am Ind Hyg Assoc J 59(2):96-103.

*Werley MS, Ballantyne B, Neptun DA, et al. 1996. Four-week repeated skin contact study with glutaraldehyde in rats. J Toxicol Cutaneous Ocul Toxicol 15(2):179-193.

*Werley MS, Burleigh-Flayer HD, Ballantyne B. 1995. Respiratory peripheral sensory irritation and hypersensitivity studies with glutaraldehyde vapor. Toxicol Ind Health 11(5):489-501.

*West AB, Kuan SF, Bennick M, et al. 1995. Glutaraldehyde colitis following endoscopy: clinical and pathological features and investigation of an outbreak. Gastroenterology 108(4):1250-1255.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 24, 2013.

*WHO. 2011. Guidelines for drinking-water quality. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html. April 24, 2013.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advance treatise. Volume II: The elements Part A. New York, NY: Academic Press, 1-247.

*Wilcox P, Naidoo A, Wedd DJ, et al. 1990. Comparison of Salmonella typhimurium TA102 with Escherichia coli WP2 tester strains. Mutagenesis 5(3):285-291.

*Winslow RM. 2003. Blood substitutes. In: Kirk-Othmer encyclopedia of chemical technology. http://onlinelibrary.wiley.com/doi/10.1002/0471238961.0212151523091419.a01.pub2/abstract. April 6, 2014.

*Wu A, Schmalz J, Bennett W. 1994. Identification of UrinAid-adulterated urine specimens by fluorometric analysis. Clin Chem 40(5):845-846.

*Wulff K, Henniger G. 2012. Enzymes, 7. Enzymes in analysis. In: Ullmann's encyclopedia of industrial chemistry. http://onlinelibrary.wiley.com/doi/10.1002/14356007.m09_m06/abstract. April 6, 2014.

*Yamaguchi F, Tsutsui T. 2003. Cell-transforming activity of fourteen chemical agents used in dental practice in Syrian hamster embryo cells. J Pharmacol Sci 93:497-500.

*Yoon JS, Mason JM, Valencia R, et al. 1985. Chemical mutagenesis testing in drosophila. IV. Results of 45 coded compounds tested for the national toxicology program. Environ Mutagen 7:349-367.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12(1):29-34.

*Zeiger E, Gollapudi B, Spencer P. 2005. Genetic toxicity and carcinogenicity studies of glutaraldehyde-a review. Mutat Res 589(2):136-151.

*Zimmering S, Mason JM, Valencia R. 1989. Chemical mutagenesis testing in Drosophila: VII. Results of 22 coded compounds tested in larval feeding experiments. Environ Mol Mutagen 14(4):245-251.

*Zissu D, Bonnet P, Binet S. 1998. Histopathological study in B6C3F1 mice chronically exposed by inhalation to glutaraldehyde. Toxicol Lett 95(2):131-139.

*Zissu D, Gagnaire F, Bonnet P. 1994. Nasal and pulmonary toxicity of glutaraldehyde in mice. Toxicol Lett 71(1):53-62.

9. REFERENCES

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: December 2015
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 0.001 [ ] mg/kg/day [x] ppm

References:

Gross EA, Mellick PW, Kari FW, et al. 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(3):348-362.

NTP. 1993. NTP Technical report on toxicity studies of glutaraldehyde (CAS No. 111-30-8) administered by inhalation to F344/N tats and B6C3F1 mice. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. 25. NIH Publication 93-3348, Number 25.

Experimental design: In a study designed to evaluate the time course of glutaraldehyde-induced nasal lesions, male and female F344 rats and B6C3F1 mice were exposed to glutaraldehyde vapor for 6 hours/day for 1 or 4 days, or 6 or 13 weeks at glutaraldehyde vapor concentrations of 0.0625, 0.125, 0.250, 0.5, or 1 ppm and sacrificed for evaluation of exposure-related nasal lesions.

Effect noted in study and corresponding doses: Exposure-related increased incidences of rats and mice exhibiting selected nasal lesions were observed following exposure to glutaraldehyde vapor at 0.250 ppm 6 hours per day for as little as 1 or 4 days; there were no apparent exposure-related effects on nasal lesion incidences at 0.125 ppm (Table A-1). This study identified a NOAEL of 0.125 ppm, and the lowest LOAEL (0.25 ppm for histopathological nasal lesions) among the acute-duration inhalation studies and was therefore selected as the principal study for derivation of an acute-duration inhalation MRL for glutaraldehyde.

Table A-1. Incidences of Male and Female F344 Rats and B6C3F1 Mice with Selected Histopathologic Nasal Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day for 1 or 4 Days[a]

Species (gender)	Exposure level (ppm)	Squamous exfoliation		Intraepithelial neutrophils		Subepithelial neutrophils		Epithelial erosions	
		1 day	4 days	1 day	4 days	1 day	4 days	1 day	4 days
Rat (male)	0	0/5	0/5	0/5	0/5	0/5	1/5 (0.2)[b]	0/5	0/5
	0.0625	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/4	0/5	0/4	0/5	0/4	2/5 (0.4)	0/4	0/5
	0.250	1/5	0/5	1/5 (0.4)	0/5	3/5 (0.8)	1/5 (0.2)	1/5	1/5
	0.500	3/5	3/5	2/5 (0.4)	5/5 (1.4)	5/5 (1.8)	5/5 (1.6)	5/5	2/5
	1.00	5/5	5/5	5/5(1.2)	5/5 (2.6)	5/5 (2.6)	5/5 (3.4)		5/5
Rat (female)	0	0/5	0/5	0/5	1/5 (0.2)	0/5	2/5 (0.4)	0/5	0/5
	0.0625	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	0/5	0/5	1/5 (0.4)	0/5	1/5	0/5
	0.250	2/5	3/5	0/5	2/5 (0.4)	1/5 (0.2)	4/5 (1.4)	0/4	2/5
	0.500	3/5	5/5	2/5 (0.6)	5/5 (2.2)	5/5 (2.4)	5/5 (2.8)	4/5	3/5
	1.00	4/5	5/5	4/5 (1.0)	5/5 (3.4)	5/5 (2.8)	5/5 (3.8)		5/5
Mouse (male)	0	0/5	0/5	1/5 (0.2)	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.0625	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	1/5 (0.2)	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.250	0/5	4/5	0/5	1/5 (0.2)	1/5 (0.2)	2/5 (0.4)	0/5	0/5
	0.500	4/5	2/5	1/5 (0.2)	4/5 (1.8)	2/5 (0.4)	4/5 (1.8)	1/5	1/5
	1.00	5/5	5/5	5/5 (1.0)	5/5 (2.8)	5/5 (1.6)	5/5 (3.2)	2/5	2/5
Mouse (female)	0	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.0625	0/5	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.250	0/5	2/5	0/5	1/5 (0.4)	0/5	1/5 (0.4)	0/5	0/5
	0.500	5/5	5/5	0/5	5/5 (1.0)	2/5 (0.4)	5/5 (1.6)	0/5	0/5
	1.00	4/5	5/5	1/5 (0.4)	4/5 (0.8)	3/5 (1.2)	5/5 (2.0)	1/5	2/5

[a]Gray shaded cells suggest a toxicologically significant increased incidence from controls.
[b]Severity (in parentheses) is the mean for all animals in a group where: 0 = no lesion; 1 = minimal; 2 = mild; 3 = moderate; and 4 = marked.

Sources: Gross et al. 1994; NTP 1993

Dose and end point used for MRL derivation: 0.125 ppm (adjusted for continuous exposure and converted to a human equivalent concentration resulting in a $NOAEL_{HEC}$ of 0.003 ppm)

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 1 for extrapolation from animals to humans using dosimetric conversion

[x] 3 for human variability

An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for human variability consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Derivation of a HEC based on the $NOAEL_{ADJ}$ was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde) using the following equation:

$RGDR_{ET} = (VE/SA_{ET})_A / (VE/SA_{ET})_H$ [equation 4-18 in EPA 1994]

where:

RGDR = ratio of the regional gas dose in animals to that of humans
VE = minute volume (cm^3/minute)
SA = surface area (cm^2)
$_{ET}$ = extrathoracic
$_A$ = animal
$_H$ = human

EPA-reported SA_{ET} values for rats (15 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). Minute volumes were taken from Table 1-4 of EPA (1988) in which they were presented as m^3/day (0.14 m^3/day = 97.2 cm^3/minute for subchronic exposure of the female F344 rat). Subchronic values were used because the rats were approximately 6–7 weeks old at the initiation of exposures. According to EPA (1994), the default minute volume for humans is 13,800 cm^3/minute. Therefore:

$RGDR_{ET}$ (rat) = (97.2 mL/minute/15 cm^2) / (13,800 mL/minute/200 cm^2) = 6.48/69 = 0.0939

The human equivalent NOAEL was calculated according to the following equation:

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RGDR_{ET}$ (rat) = 0.031 ppm x 0.0939 = 0.003 ppm ($3x10^{-3}$ ppm)

Was a conversion used from intermittent to continuous exposure? The 6-hour exposure was converted to a continuous exposure scenario by multiplying the 6-hour NOAEL of 0.125 ppm by 6 hours/24 hours, resulting in a $NOAEL_{ADJ}$ of 0.031 ppm. The adjustment to account for continuous exposure scenarios is necessary because nasal lesions were observed in glutaraldehyde-exposed rats and mice at lower exposure levels following 6 or 13 weeks of repeated 6-hour exposures than those eliciting nasal lesions following a single 6-hour exposure or repeated 6-hour exposures on 4 consecutive days.

Other additional studies or pertinent information that lend support to this MRL: In a study of Union Carbide Corp (1992d), rhinitis and mild atrophy of the olfactory mucosa were observed in male and female F344 rats exposed to glutaraldehyde vapor at 3.1 ppm for 6 hours/day for 9 exposures in 11 days; at an exposure level of 1.1 ppm, males (but not females) exhibited rhinitis and mild squamous metaplasia of the olfactory mucosa. This study identified a NOAEL of 0.3 ppm and a LOAEL of 1.1 ppm for nasal lesions in the male rats. Zissu et al. (1994) observed histopathological lesions in the respiratory epithelium of septum and naso- and maxilloturbinates of male Swiss OF1 mice exposed to glutaraldehyde vapor for 5 hours/day on 4 consecutive days at 0.3 ppm (the lowest concentration tested); the severity of glutaraldehyde-induced nasal lesions increased with increasing exposure concentration. This study did not identify a NOAEL.

Agency Contacts (Chemical Managers): Sharon Wilbur, M.A.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: December 2015
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 37
Species: Mouse

Minimal Risk Level: 0.00003 [ ] mg/kg/day [x] ppm

References:

Gross EA, Mellick PW, Kari FW, et al. 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(3):348-362.

NTP. 1993. NTP Technical report on toxicity studies of glutaraldehyde (CAS No. 111-30-8) administered by inhalation to F344/N rats and B6C3F1 mice. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. 25. NIH Publication 93-3348, Number 25.

Experimental design: Groups of male and female B6C3F1 mice (10/sex/group) were exposed to glutaraldehyde vapor for 6 hours/day, 5 days/week, for 13 weeks at concentrations of 0, 0.0625, 0.125, 0.25, 0.5, or 1.0 ppm and evaluated for survival, clinical signs, body weight, selected organ and tissue weights, and gross and histopathology (particularly the nasal cavity).

Effect noted in study and corresponding doses: Concentration-related increased incidence and severity of clinical signs of respiratory irritation and histopathologic nasal lesions (exfoliation, inflammation, hyperplasia, and ulceration of nasal squamous epithelium; granulocytes and necrosis in nasal passages; laryngeal squamous metaplasia; necrosis in nasal nares) were reported. Histopathologic nasal lesions were sometimes noted at exposure levels lower than those resulting in overt clinical signs of respiratory tract irritation. In general, glutaraldehyde-induced histopathologic respiratory tract lesions were confined to the anterior nasal cavity and were not observed in lower respiratory tract regions. Incidence data for selected nonneoplastic nasal lesions in the male and female B6C3F1 mice are presented in Table A-2. The incidence data for inflammation in the nasal vestibule/anterior nares of the B6C3F1 female mice from the core study (NTP 1993) were selected to serve as the basis for deriving an intermediate-duration inhalation MRL for glutaraldehyde because this lesion exhibited the lowest effect level (0.0625 ppm). All dichotomous models in the BMDS (Version 2.2) were fit to the incidence data for inflammation in the nasal vestibule/anterior nares of the female mice; the highest exposure group was dropped because the incidence of inflammation in this group was not reported (the study authors stated that “inflammation was a component of ‘squamous exfoliation’ and not diagnosed separately when the latter was present”). A BMR of 10% extra risk was applied. The results of the BMD analysis are summarized in Table A-3.

Table A-2. Incidences of Male and Female B6C3F1 Mice Exhibiting Selected Histopathologic Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks in the Core Study of NTP (1993)[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Males						
Nasal passages/turbinates						
Respiratory epithelium						
Inflammation	0	0	0	0	0	4(1.0)[b]
Squamous metaplasia	0	0	0	0	0	1 (1.2)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1 (1.0)	2 (1.0)	9 (2.8)[c]
Inflammation	0	0	0	0	7 (1.1)[c]	0[d]
Erosion	0	0	0	1 (1.0)	1 (1.0)	0
Larynx						
Squamous metaplasia	0	0	0	0	0	7 (1.6)[c]
Necrosis	0	0	0	0	0	2 (1.0)
Females						
Nasal passages/turbinates						
Respiratory epithelium						
Inflammation	0	0	0	0	1 (1.0)	7 (1.4) [c]
Squamous metaplasia	0	0	0	0	0	3 (1.0)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1 (1.0)	2 (2.5)	10 (2.8)[c]
Inflammation[e]	0	5 (1.0)[b]	8 (2.0)[c]	8 (1.6)[c]	8 (2.5)[c]	0[d]
Erosion	0	0	1 (1.0)	0	0	0
Larynx						
Squamous metaplasia	0	0	0	0	0	10 (1.6)[c]
Necrosis	0	0	0	0	0	2 (1.0)

[a]Incidence is the number of core-study animals with lesions for groups of 10 animals. Average severity (in parentheses) is based on the number of animals with lesions: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).
[d]Inflammation was a component of "squamous exfoliation" and not diagnosed separately when the latter was present.
[e]Gray-shaded cells depict the lesion incidence data that were subjected to benchmark dose (BMD) analysis.

Source: NTP 1993

Table A-3. Results from BMD Analysis of Incidences of Female B6C3F1 Mice Exhibiting Inflammation in the Nasal Vestibular/Anterior Nares Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks

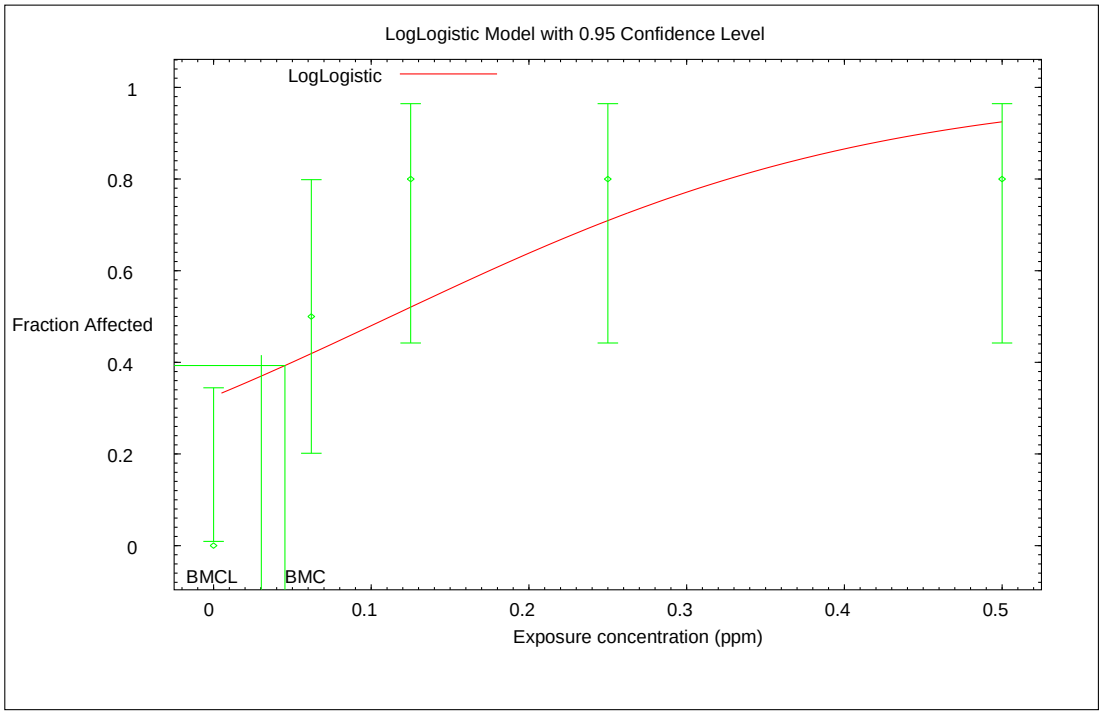
Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Logistic	3	10.88	0.01	-2.20	0.52	-2.20	61.44		
LogLogistic[d,e]	**4**	**1.63**	**0.80**	**0.00**	**-0.09**	**-0.98**	**47.40**	**0.0065**	**0.0034**
LogProbit[d]	4	8.81	0.07	0.00	0.85	-2.60	51.54		
Multistage (1-degree)[f]	4	10.75	0.03	0.00	0.12	-2.67	53.34		
Multistage (2-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Multistage (3-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Multistage (4-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Probit	3	10.99	0.01	-2.26	0.50	-2.26	61.92		
Weibull[c]	4	10.75	0.03	0.00	1.12	-2.67	53.34		

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The LogLogistic model was the only model providing adequate fit to the data.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; DF = degree of freedom

The Gamma, Logistic, LogProbit, Multistage, Probit, and Weibull models failed to meet conventional goodness-of-fit criteria because their χ^2 p-values were <0.1. The LogLogistic model provided adequate fit to the data (χ^2 p-value = 0.80, largest scaled residual -0.98), a BMC_{10} of 0.0065 ppm, and a $BMCL_{10}$ of 0.0034 ppm. Figure A-1 plots predicted incidences of the female mice exhibiting inflammation in the nasal vestibule/nares from the LogLogistic model and observed incidence values from data in Table A-3.

Figure A-1. Predicted and Observed Incidence of Female Mice Exhibiting Inflammation in the Nasal Vestibular/Anterior Nares Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks.*



*BMC and BMCL are associated with a 10% extra risk change from control

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.0034 ppm.

[ ] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 1 for extrapolation from animals to humans using dosimetric conversion
[x] 3 for human variability

An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for human variability consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Derivation of a human equivalent concentration (HEC) based on the $BMCL_{ADJ}$ was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde) using the following equation:

$RGDR_{ET} = (VE/SA_{ET})_A / (VE/SA_{ET})_H$ [equation 4-18 in EPA 1994]

where:

RGDR = ratio of the regional gas dose in animals to that of humans
VE = minute volume (cm^3/minute)
SA = surface area (cm^2)
$_{ET}$ = extrathoracic
$_A$ = animal
$_H$ = human

EPA-reported SA_{ET} values for mice (3 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). Minute volumes were taken from Table 1-4 of EPA (1988) in which they were presented as m^3/day (0.04 m^3/day = 27.8 cm^3/minute for subchronic exposure of the female B6C3F1 mouse). According to EPA (1994), the default minute volume for humans is 13,800 cm^3/minute. Therefore:

$RGDR_{ET}$ (mouse) = (27.8 mL/minutes/3 cm^2) / (13,800 mL/minutes/200 cm^2) = 9.27/69 = 0.134

The human equivalent $BMCL_{10}$ was calculated according to the following equation:

$BMCL_{10HEC} = BMCL_{10ADJ}$ x $RGDR_{ET}$ (mouse) = 0.0006 ppm x 0.134 = 0.00008 ppm ($8x10^{-5}$ ppm)

Was a conversion used from intermittent to continuous exposure? The 6-hour/day, 5 days/week exposure was converted to a continuous exposure scenario by multiplying the $BMCL_{10}$ of 0.0034 ppm by 6 hours/24 hours and 5 days/7 days, resulting in a $BMCL_{10ADJ}$ of 0.0006 ppm.

The adjustment to account for continuous exposure scenarios is necessary because nasal lesions were observed in glutaraldehyde-exposed rats and mice at lower exposure levels following 6 or 13 weeks of repeated 6-hour exposures than those eliciting nasal lesions following a single 6-hour exposure or repeated 6-hour exposures on 4 consecutive days.

Other additional studies or pertinent information that lend support to this MRL: The principal study (Gross et al. 1994; NTP 1993) included groups of male and female F344/N rats exposed to glutaraldehyde vapor for 6 hours/day, 5 days/week, for 13 weeks at 0.0625, 0.125, 0.250, 0.5, or 1 ppm as well. Nasal lesions similar to those observed in the mice were also noted in the rats (see Table A-4). In a similarly-designed histopathology time-course study that evaluated the progression of nasal lesions for up to 13 weeks (5/species/sex/exposure group/time point) (Gross et al. 1994; NTP 1993), neutrophilic infiltration into intra- and subepithelial regions of the nasal vestibule of female mice was identified as the most sensitive effect and was observed at the lowest exposure level tested (0.0625 ppm) (see Table A-5). The neutrophilic infiltration was consistent with inflammation in the core study, thus providing support to the findings of the core study.

Table A-4. Incidences of Male and Female F344/N Rats Exhibiting Selected Histopathologic Nasal Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks in the Core Study of NTP (1993)[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Males						
Respiratory epithelium						
Nasoturbinates/septum						
Hyperplasia	0	0	0	0	0	7 (1.7)[b]
Hyperplasia, goblet cell	0	0	0	1 (1.0)	3 (1.0)	9 (1.4)[b]
Squamous metaplasia	0	0	0	0	0	5 (2.0)[c]
Inflammation	0	0	0	0	0	7 (1.0)[b]
Lateral wall						
Hyperplasia	0	0	1 (1.0)	0	4 (1.0)[c]	7 (1.7)[b]
Squamous metaplasia	0	0	0	0	1 (1.0)	7 (2.5)[b]
Olfactory epithelium						
Degeneration	0	0	0	0	0	1 (2.0)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1(1.0)	4 (1.0)[c]	9 (1.1)[b]
Inflammation	0	1 (1.0)	0	0	0	3 (1.0)
Females						
Respiratory epithelium						
Nasoturbinates/septum						
Hyperplasia	0	0	0	0	0	4 (1.7)[c]
Hyperplasia, goblet cell	0	0	0	0	0	8 (1.2)[b]
Squamous metaplasia	0	0	0	0	0	5 (1.4)[c]
Inflammation	0	0	0	1 (1.0)	0	5 (1.2)[c]
Lateral wall						
Hyperplasia	0	0	0	1 (2.0)	2 (1.0)	8 (1.6)[b]
Squamous metaplasia	0	0	0	1 (3.0)	0	8 (2.0)[b]
Olfactory epithelium						
Degeneration	0	0	0	0	0	2 (1.5)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	3 (1.3)	7 (1.1)[b]	9 (1.7)[b]
Inflammation	1 (1.0)	0	0	0	0	0
Erosion	0	0	0	0	1 (1.0)	2 (2.0)

[a]Incidence is the number of core-study animals with lesions for groups of 10 animals. Average severity (in parentheses) is based on the number of animals with lesions: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).

Source: NTP 1993

Table A-5. Incidences of Male and Female F344/N Rats and B6C3F1 Mice Exhibiting Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week For 13 Weeks in the Histopathology Time-Course Study[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Male rat						
Squamous exfoliation	0	0	0	2	2	2
Intraepithelial neutrophils	5 (1.2)[b]	3 (0.8)	5 (1.0)	5 (1.2)	4 (1.2)	5 (1.6)
Subepithelial neutrophils	5 (1.0)	4 (1.0)	5 (1.2)	5 (1.6)	5 (1.4)	5 (2.0)
Epithelial erosions	1	1	0	1	1	1
Squamous metaplasia	1 (0.2)	0	0	0	5 (2.0)	5 (3.0)
Female rat						
Squamous exfoliation	0	0	0	0	2	4
Intraepithelial neutrophils	1 (0.2)	0	1 (0.4)	3 (1.0)	2 (0.8)	4 (1.4)
Subepithelial neutrophils	2 (0.4)	0	1 (0.8)	3 (1.0)	4 (1.8)	4 (2.0)
Epithelial erosions	0	0	0	0	0	1
Squamous metaplasia	0	0	0	0	3 (1.2)	5 (2.6)
Male mouse						
Squamous exfoliation	0	0	0	3	1	–[c]
Intraepithelial neutrophils	0	0	1 (0.2)	4 (1.6)	5 (2.6)	–
Subepithelial neutrophils	0	1 (0.2)	2 (0.8)	5 (2.2)	5 (2.8)	–
Epithelial erosions	0	0	0	1	3	–
Squamous metaplasia	0	0	0	0	1 (0.2)	–
Female mouse						
Squamous exfoliation	0	0	0	0	1/4	–
Intraepithelial neutrophils	0	4 (2.0)	5 (2.4)	5 (3.2)	4/4 (2.8)	–
Subepithelial neutrophils	2 (0.4)	5 (2.0	5 (2.8)	5 (3.2)	4/4 (2.8)	–
Epithelial erosions	0	0	0	0	0/4	–
Squamous metaplasia	0	0	0	0	1/4 (0.5)	–

[a]Gray shaded cells suggest a toxicologically significant increased incidence from controls.
[b]Incidence is the number of animals with lesions for groups of five animals unless a denominator is given. Severity (in parentheses) was averaged for five animals/group where: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[c]Not evaluated, all animals died.

Sources: Gross et al. 1994; NTP 1993

Agency Contacts (Chemical Managers): Sharon Wilbur, M.A.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: December 2015
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 46
Species: Rat

Minimal Risk Level: 0.1 [x] mg/kg/day [ ] ppm

Reference: van Miller JP, Hermansky SJ, Losco PE, et al. 2002. Chronic toxicity and oncogenicity study with glutaraldehyde dosed in the drinking water of Fischer 344 rats. Toxicology 175(1-3):177-189.

Experimental design: In a 2-year chronic toxicity and oncogenicity study, Fischer 344 rats (100/sex/group) were administered glutaraldehyde (50.0–51.3% w/w aqueous solution) in the drinking water at concentrations of 0, 50, 250, or 1,000 ppm for 52 weeks (first interim sacrifice of 10/sex/group), 78 weeks (second interim sacrifice of 10/sex/group), or up to 104 weeks (main group). Author-reported average glutaraldehyde doses were 0, 4, 17, and 64 mg/kg/day, respectively, for the males and 0, 6, 25, and 86 mg/kg/day, respectively, for the females. Animals were observed for survival, clinical signs, body weight, and food and water consumption. Eyes were examined by indirect ophthalmoscopy before the start of dosing and after weeks 52, 78, and 104. Hematology and serum chemistry evaluations were performed at weeks 12, 26, 52, 78, and 104 (10 rats/sex/group). Urine was collected from 10 rats/sex/group during weeks 12, 25, 51, 77, and 103 for urinalysis. All surviving rats were sacrificed at week 104. At sacrifice, liver, kidneys, brain, heart, adrenal glands, and testes were removed and weighed. Comprehensive gross and histopathologic examinations were performed on all animals.

Effect noted in study and corresponding doses: Treatment-related effects included slightly depressed body weight and lesions of the stomach. The depressions in body weight were typically <10% in magnitude. Gross pathology revealed gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa) in 250- and 1,000-ppm male and female rats at 52-, 78-, and 104-week sacrifice (prevalences of 30, 10–20, and 10%, respectively) and in animals that died prior to scheduled sacrifice (prevalence of 40%). Histopathology revealed significantly increased incidences of 1,000-ppm male and female rats with mucosal hyperplasia in the stomach at terminal sacrifice (males: 7/51 versus 1/56 controls; females 7/56 versus 1/62 controls), but not at 52- or 78-week interim sacrifices. Incidences of this lesion at the lower dose levels were not significantly different from those of controls. This study identified NOAELs of 4 and 6 mg/kg/day for the male and female rats, respectively, and LOAELs of 17 and 25 mg/kg/day for male and female rats, respectively, for gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa).

Dose and end point used for MRL derivation: 4 mg/kg/day

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans

[x] 3 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Wistar rats (50/sex/group) were administered glutaraldehyde (50.5% active ingredient) in the drinking water for up to 24 months at concentrations of 0, 100, 500, or 2,000 ppm (approximate daily glutaraldehyde intakes of 0, 3, 16, and 60 mg/kg/day, respectively, for the males and 0, 5, 24, and 88 mg/kg/day, respectively, for the females) (BASF 2013; Confidential 2002). Increased incidences of non-neoplastic lesions were observed at the 2,000 ppm exposure level and involved the larynx (squamous metaplasia in males [18/50 versus 0/50 controls] and females [30/50 versus 0/50 controls]) and trachea (squamous metaplasia in males [4/50 versus 0/50 controls] and females [11/50 versus 0/50 controls]). In addition, significant trends for increasing incidence with increasing glutaraldehyde concentration were noted for diffuse metaplasia in the larynx of male and female rats, focal metaplasia in the larynx of females, focal squamous metaplasia in the trachea of males and females, and diffuse metaplasia in the trachea of females. Metaplasia was nearly always accompanied by accumulation of keratin detritus in the laryngeal and/or tracheal lumen. Some high-dose rats with laryngeal/tracheal metaplasia also exhibited foreign body granulomas in the lung and/or inflammation in the tracheal lumen. Significantly increased incidence of erosion/ulceration was noted in the glandular stomach of 2,000-ppm females. Purulent inflammation in the nasal cavity was seen in three males and six females of the highest exposure level.

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APPENDIX B. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR GLUTARALDEHYDE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to glutaraldehyde, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013a; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to glutaraldehyde:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

B.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to glutaraldehyde. The inclusion criteria used to identify relevant studies examining the health effects of glutaraldehyde are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

B.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of glutaraldehyde. Studies for other sections of the toxicological profile were also identified in the literature search and screen step. Although these studies were not included in the systematic review process, the results of some studies (e.g., mechanistic studies, toxicokinetic studies) were considered in the final steps of the systematic review. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of glutaraldehyde have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Cancer

B.2.1 Literature Search

The following databases were searched, without date restrictions, in January 2013:

- PubMed
- National Library of Medicine's TOXLINE
- Scientist and Technical Information Network's TOXCENTER
- National Pesticide Information Retrieval System (NPIRS)
- Toxic Substances Control Act Test Submissions (TSCATS) and TSCATS2

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

The search strategy used the chemical name, CAS number (i.e., 111-30-8), synonyms, and Medical Subject Headings (MeSH) terms for glutaraldehyde. A total of 5,197 records were identified and imported into EndNote (version 5). After the identification and removal of 1,850 duplicates by EndNote, the remaining 3,337 records were moved to the literature screening step.

B.2.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies examining the health effects of glutaraldehyde:

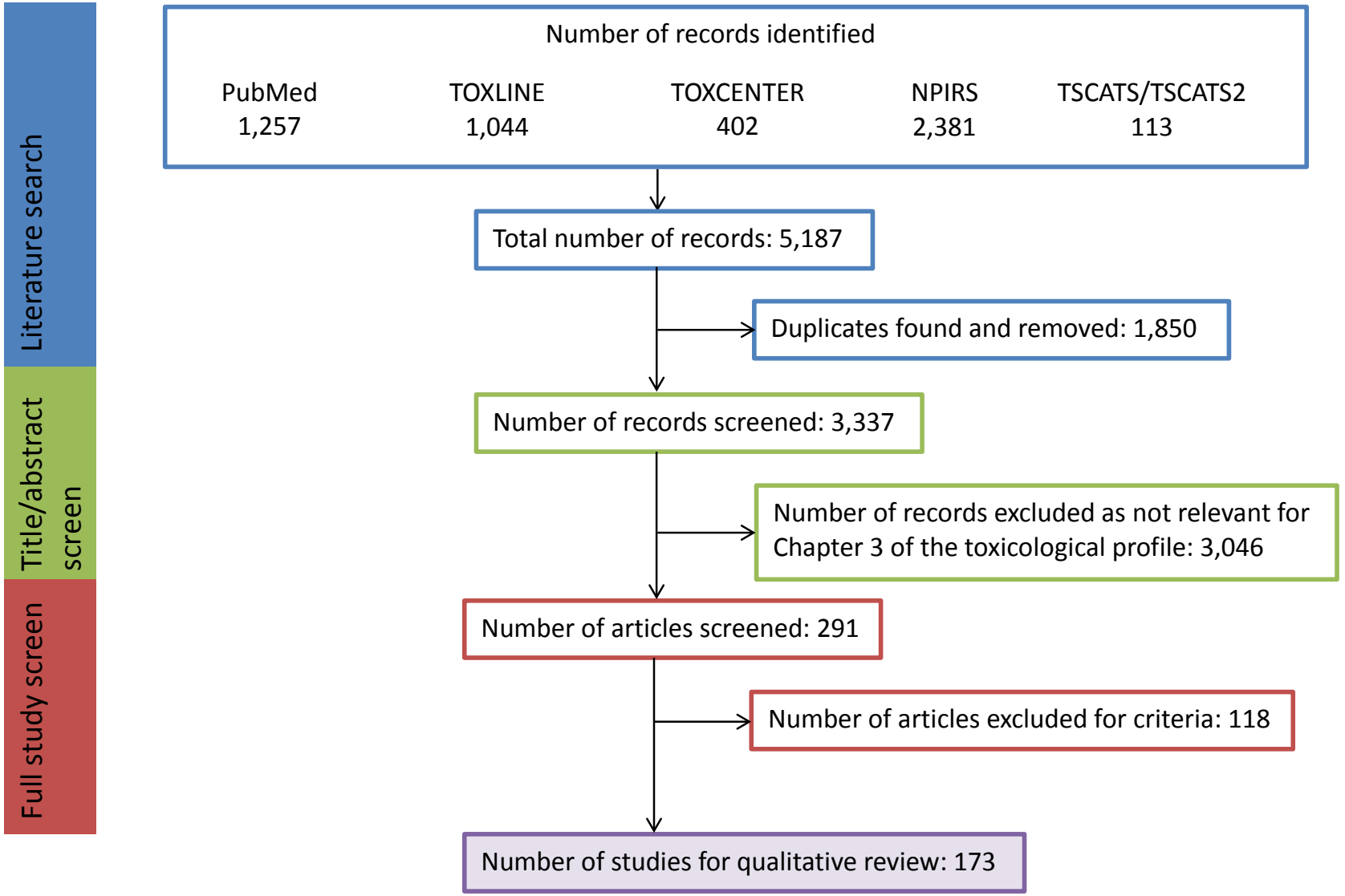
- Title and Abstract Screen
- Full Text Screen

Title and Abstract Screen. Within the Endnote library, titles and abstracts were screened manually for relevance. Studies that were considered relevant were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study did not meet the inclusion criteria (Table B-1). In the Title and Abstract Screen step, 3,337 records were reviewed; 291 studies were considered relevant to Chapter 3 of the toxicological profile and were moved to the next step in the process.

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the Title and Abstract Screen step. Each study was reviewed to determine whether it met the inclusion criteria; however, the quality of the studies was not evaluated at this step of the process. Of the 291 studies undergoing Full Text Screen, 118 studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. Literature Search and Screen for Glutaraldehyde Health Effect Studies



B.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms in Distiller. A summary of the type of data extracted from each study is presented in Table B-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Document for Glutaraldehyde and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Section 3.2 of the profile and in the Levels Significant Exposures tables in Section 3.2 of the profile (Tables 3-1, 3-7, and 3-8, respectively).

B.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for glutaraldehyde identified in human and animal studies are presented in Tables B-3 and B-4, respectively. The available human studies examined a limited number of end points and reported respiratory, dermal, and ocular effects. Animal studies examined a number of end points following inhalation, oral, and dermal/ocular exposure. These studies reported respiratory, gastrointestinal, hematological, renal, dermal, ocular, body weight, and developmental effects. The hematological effects that were observed in one intermediate-duration inhalation exposure animal study were considered to be secondary to the nasal effects or were of questionable toxicological relevance due to the small magnitude of change. The body weight effects were not considered a primary effect and were likely secondary to the morbidity associated with the respiratory, gastrointestinal, or dermal effects. Similarly, the developmental effects appear to be secondary to maternal lethality (inhalation study) or taste aversion to glutaraldehyde-containing water. Thus, the available human and animal studies identify five potential health outcomes for glutaraldehyde: respiratory, gastrointestinal, renal, dermal, and ocular effects; the evidence streams for these outcomes were continued through Steps 5–8 of the systematic review. Animal studies have examined other potential end points, but did not find effects. For example, 16 animal studies examined the liver, but none of the studies reported an adverse effect. In the absence of human studies examining these potential outcomes, these data were considered inadequate for assessing the human hazard potential and were not continued through the systematic review process.

Table B-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

Table B-3. Overview of the Health Outcomes for Glutaraldehyde Evaluated In Human Studies

	Systemic effects												Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Other					
Inhalation studies																	
Cohort	6 6																
Case control																	
Population																	
Controlled exposure	3 3																
Oral studies																	
Cohort																	
Case control																	
Population																	
Controlled exposure																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Controlled Exposure									2 2	1 1							

Number of studies examining end point	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

Table B-4. Overview of the Health Outcomes for Glutaraldehyde Evaluated in Experimental Animal Studies

	Systemic effects												Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Other					
Inhalation studies																	
Acute-duration	11 11										3 2		2 0	2 0			
Intermediate-duration	8 7	2 0		2 1		3 0	2 0				2 2			2 0	2 0		
Chronic-duration	2 2	2 0	2 0	2 0		2 0	2 0	2 0			2 1			2 0	2 0		
Oral studies																	
Acute-duration			7 7	1 0		7 0	6 2				9 1					7 0	
Intermediate-duration	3 0		1 1	4 0		3 0	4 3			3 0	5 1				1 0	1 0	
Chronic-duration	1 1		2 2	1 0		1 0	1 0				1 1						
Dermal studies																	
Acute-duration									7 7	5 5	1 1						
Intermediate-duration																	
Chronic-duration																	

Number of studies examining end point	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

B.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

B.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's risk of bias questions (Rooney et al. 2014) and guidance for assessing risk of bias (NTP 2013b). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables B-5, B-6, and B-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table B-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance bias
Did researchers adhere to the study protocol?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Were the outcome assessors blinded to study group or exposure level?
Were the confounding variables assessed consistently across groups using valid and reliable measures?
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table B-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Confounding bias

Did the study design or analysis account for important confounding and modifying variables?

Did researchers adjust or control for other exposures that are anticipated to bias results?

Performance bias

Did researchers adhere to the study protocol?

Were the research personnel and human subjects blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Were the outcome assessors blinded to study group or exposure level?

Were the confounding variables assessed consistently across groups using valid and reliable measures?

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

Table B-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Confounding bias

Did the study design or analysis account for important confounding and modifying variables?

Did researchers adjust or control for other exposures that are anticipated to bias results?

Performance bias

Were experimental conditions identical across study groups?

Did researchers adhere to the study protocol?

Were the research personnel blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Were the outcome assessors blinded to study group or exposure level?

Were the confounding variables assessed consistently across groups using valid and reliable measures?

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of glutaraldehyde health effects studies (observational epidemiology, human experimental, and animal experimental studies) are presented in Tables B-8, B-9, and B-10, respectively.

Table B-8. Summary of Risk of Bias Assessment for Glutaraldehyde—Observational Epidemiology Studies

	Risk of bias criteria and ratings										
	Selection bias	Confounding bias		Performance bias	Attrition / exclusion bias	Detection bias				Selective reporting bias	
Reference	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Did researchers adhere to the study protocol?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects											
Cross-sectional cohort studies											
NIOSH 1987a	na	–	–	+	+	+	na	+	+	+	Second
NIOSH 1987b	na	–	–	+	+	+	na	+	+	+	Second
Pisaniello et al. 1997	+	–	–	+	+	+	na	+	+	+	Second
Cohort studies											
Norbäck 1988	+	+	–	+	+	+	na	+	+	+	First
Vyas et al. 2000	+	–	–	+	+	+	na	+	+	+	Second
Waters et al. 2003	+	–	–	+	+	+	na	+	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

Table B-9. Summary of Risk of Bias Assessment for Glutaraldehyde—Human-Controlled Exposure Studies

	Risk of bias criteria and ratings												
	Selection bias		Confounding bias		Performance bias		Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects													
Inhalation acute exposure													
Union Carbide Corp. 1976	+	na	+	+	+	+	++	na	na	+	+	+	First
Cain et al. 2007	+	na	+	+	+	+	++	na	na	+	+	+	First
Outcome: Dermal effects													
Dermal acute exposure													
Union Carbide Corp. 1966	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1980	+	+	+	+	+	+	+	+	+	+	+	+	First
Outcome: Ocular effects													
Ocular acute exposure													
Cain et al. 2007	+	na	+	+	+	+	++	na	na	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects														
Inhalation acute exposure														
Werley et al. 1995 (mouse)	+	+	+	+	++	+	+	+	+	+	++	++	+	First
Werley et al. 1995 (guinea pig)	+	+	+	+	+	+	+	+	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Zissu et al. 1994 (mouse)	+	+	+	+	+	+	+	+	+	na	++	++	+	First

APPENDIX B

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Zissu et al. 1994 (mouse)	+	+	+	+	+	+	+	+	+	na	++	++	+	First
Union Carbide Corp. 1992l (rat)	++	+	+	+	+	+	+	+	+	+	++	+	++	First
Union Carbide Corp. 1992d (rat)	++	+	+	+	+	+	+	++	+	+	++	++	++	First
Union Carbide Corp. 1992e (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure														
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Union Carbide Corp. 1992f (rat)	++	+	+	+	+	+	+	++	+	+	++	++	++	First
Inhalation chronic exposure														
NTP 1999; van Birgelen et al. 2000 (rat)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999 (rat)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999; van Birgelen et al. 2000 (mouse)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999 (mouse)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
Outcome: Gastrointestinal effects														
Oral acute exposure														
BASF Corp. 1990l (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
BASF Corp. 1990m (rabbit)	+	+	+	+	+	+	+	++	+	+	+	+	+	First
BASF Corp. 1991a (rabbit)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
BASF Corp. 1991c (rat)	+	+	+	+	++	++	+	+	+	+	++	++	++	First
Union Carbide Chem & Plas Co. 1992 (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992a (rat)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992i (mouse)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Chem & Plas Co. 1991dd (dog)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure														
Union Carbide	+	+	+	+	+	+	+	+	+	+	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Chem & Plas Co. 1991ee (dog)														
Oral chronic exposure														
van Miller et al. 2002 (rat)	+	+	+	+	+	++	+	++	+	na	+	+	+	First
Outcome: Renal effects														
Inhalation intermediate exposure														
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Oral acute exposure														
BASF Corp. 1990l (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
BASF Corp. 1990m (rabbit)	+	+	+	+	+	+	+	++	+	+	+	+	+	First
BASF Corp. 1991c (rat)	+	+	+	+	++	++	+	+	+	+	++	++	++	First
BASF Corp. 1991c (rabbit)	+	+	+	+	++	++	+	+	+	+	++	++	++	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Union Carbide Chem & Plas Co. 1991f (rat)	+	+	+	+	+	+	+	++	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991o (rat)	++	+	+	+	+	+	+	++	+	+	++	+	+	First
Oral intermediate exposure														
Union Carbide Chem & Plas Co. 1991w (mouse)	++	+	+	+	++	++	+	++	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991r (rat)	++	+	+	+	++	+	+	++	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991ee (dog)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure														
van Miller et al. 2002 (rat)	+	+	+	+	+	++	+	++	+	na	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Dermal effects														
Dermal acute exposure														
Union Carbide Chem & Plas Co. 1991y (mouse)	++	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991aa (rabbit)	na	na	+	+	++	++	na	++	na	na	+	+	+	First
Union Carbide Corp. 1992a (rabbit)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992b (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992c (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992h (rabbit)	na	na	+	+	na	+	na	+	na	na	+	+	+	First
Dermal intermediate exposure														
Werley et al. 1996	+	+	+	+	+	++	+	++	+	+	++	++	++	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
(rat)														
Outcome: Ocular effects														
Inhalation acute exposure														
Hoechst Celanese Corp. 1981 (rat)	++	+	+	+	na	+	na	++	na	na	++	++	+	First
Union Carbide Corp. 1992e (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Ocular Acute Exposure														
Union Carbide Chem & Plas Co. 1991cc (rabbit)	na	na	na	na	na	+	na	++	na	na	++	++	++	First
Union Carbide Chem & Plas Co. 1991k (rabbit)	na	na	+	+	na	+	na	+	na	na	+	+	+	First
Union Carbide Corp. 1992a (rabbit)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992b (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Union Carbide Corp. 1992c (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

B.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to glutaraldehyde and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

B.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to glutaraldehyde and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in Tables B-11, B-12, and B-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table B-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table B-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses was performed and reported or the data were reported in such a way to allow independent statistical analysis

Table B-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Were appropriate parameters used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, gastrointestinal, renal, dermal, and ocular effects observed in the observational epidemiology, human experimental, and animal experimental studies are presented in Tables B-14, B-15, and B-16, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table B-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table B-17.

Table B-14. Presence of Key Features of Study Design for Glutaraldehyde—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory effects					
Cross-sectional cohort studies					
NIOSH 1987a	No	Yes	Yes	No	Low
NIOSH 1987b	No	Yes	Yes	No	Low
Pisaniello et al. 1997	No	Yes	Yes	Yes	Moderate
Cohort studies					
Norbäck 1988	No	Yes	Yes	Yes	Moderate
Vyas et al. 2000	No	Yes	Yes	No	Low
Waters et al. 2003	No	Yes	Yes	Yes	Moderate

Table B-15. Presence of Key Features of Study Design for Glutaraldehyde—Human-Controlled Exposure Studies

Reference	Key feature				Initial study confidence
	Concurrent control group or self-control	Sufficient number of subjects tested	Appropriate methods to measure outcome	Adequate data for statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Union Carbide Corp. 1976	Yes	Yes	Yes	No	Moderate
Cain et al. 2007	Yes	Yes	Yes	No	Moderate
Outcome: Dermal effects					
Dermal acute exposure					
Union Carbide Corp. 1966	No	Yes	Yes	No	Low
Union Carbide Corp. 1980	No	Yes	Yes	No	Low
Outcome: Ocular Effects					
Ocular acute exposure					
Cain et al. 2007	Yes	Yes	Yes	No	Moderate

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Werley et al. 1995 (mouse)	Yes	No	Yes	Yes	Moderate
Werley et al. 1995 (guinea pig)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Zissu et al. 1994 (mouse)	Yes	Yes	Yes	Yes	High
Zissu et al. 1994 (mouse)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992l (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992d (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992e (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992f (rat)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
NTP 1999; van Birgelen et al. 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 1999 (rat)	Yes	Yes	Yes	Yes	High
NTP 1999; van Birgelen et al. 2000 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1999 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Gastrointestinal effects					
Oral acute exposure					
BASF Corp. 1990l (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1990m (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991a (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rat)	Yes	Yes	Yes	Yes	High

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Union Carbide Chem & Plas Co. 1992 (rat)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rat)	No	No	Yes	No	Very low
Union Carbide Corp. 1992i (mouse)	No	No	Yes	Yes	Low
Union Carbide Chem & Plas Co. 1991dd (dog)	Yes	No	Yes	No	Low
Oral intermediate exposure					
Union Carbide Chem & Plas Co. 1991ee (dog)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
van Miller et al. 2002 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects					
Inhalation intermediate exposure					
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
BASF Corp. 1990l (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1990m (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rabbit)	Yes	Yes	Yes	Yes	High
Union Carbide Chem & Plas Co. 1991f (rat)	Yes	No	Yes	No	Low
Union Carbide Chem & Plas Co. 1991o (rat)	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Union Carbide Chem & Plas Co. 1991w (mouse)	Yes	Yes	Yes	No	Moderate
Union Carbide Chem & Plas Co. 1991r (rat)	Yes	Yes	Yes	No	Moderate
Union Carbide Chem & Plas Co. 1991ee (dog)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
van Miller et al. 2002 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Dermal effects					
Dermal acute exposure					
Union Carbide Chem & Plas Co. 1991y (mouse)	Yes	No	Yes	Yes	Moderate
Union Carbide Chem & Plas Co. 1991aa (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992b (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992c (rabbit)	No	No	Yes	No	Very low

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Union Carbide Corp. 1992h (rabbit)	No	No	Yes	No	Very low
Dermal intermediate exposure					
Werley et al. 1996 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Ocular effects					
Inhalation acute exposure					
Hoechst Celanese Corp. 1981 (rat)	No	Yes	Yes	Yes	Moderate
Union Carbide Corp. 1992e (rat)	Yes	Yes	Yes	Yes	High
Ocular acute exposure					
Union Carbide Chem & Plas Co. 1991cc (rabbit)	No	Yes	Yes	Yes	Moderate
Union Carbide Chem & Plas Co. 1991k (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992b (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992c (rabbit)	No	No	Yes	No	Very low

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Human studies		
Cross-sectional cohort studies		
NIOSH 1987a	Low	
NIOSH 1987b	Low	Moderate
Pisaniello et al. 1997	Moderate	
Cohort studies		
Norbäck 1988	Moderate	
Vyas et al. 2000	Low	Moderate
Waters et al. 2003	Moderate	
Controlled exposure		
Union Carbide Corp. 1976	Moderate	Moderate
Cain et al. 2007	Moderate	
Animal studies		
Werley et al. 1995 (mouse)	Moderate	
Werley et al. 1995 (guinea pig)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	High
Zissu et al. 1994 (mouse)	High	
Zissu et al. 1994 (mouse)	High	
Union Carbide Corp. 1992l (rat)	High	
Union Carbide Corp. 1992d (rat)	High	
Union Carbide Corp. 1992e (rat)	High	
Inhalation intermediate exposure		
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
NTP 1993 (mouse)	Moderate	High
NTP 1993 (rat)	Moderate	
NTP 1993 (mouse)	High	
NTP 1993 (rat)	High	
Union Carbide Corp. 1992f (rat)	Moderate	
Inhalation chronic exposure		
Animal studies		
NTP 1999; van Birgelen et al. 2000 (rat)	High	High
NTP 1999 (rat)	High	

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1999; van Birgelen et al. 2000 (mouse)	High	
NTP 1999 (mouse)	High	
Outcome: Gastrointestinal effects		
Oral acute exposure		
Animal studies		
BASF Corp. 1990l (rat)	High	
BASF Corp. 1990m (rabbit)	High	
BASF Corp. 1991a (rabbit)	High	
BASF Corp. 1991c (rat)	High	High
Union Carbide Chem & Plas Co. 1992 (rat)	Very low	
Union Carbide Corp. 1992a (rat)	Very low	
Union Carbide Corp. 1992i (mouse)	Low	
Union Carbide Chem & Plas Co. 1991dd (dog)	Low	
Oral intermediate exposure		
Animal studies		
Union Carbide Chem & Plas Co. 1991ee (dog)	Moderate	Moderate
Oral chronic exposure		
Animal studies		
van Miller et al. 2002 (rat)	High	High
Outcome: Renal effects		
Inhalation intermediate exposure		
Animal studies		
NTP 1993 (rat)	High	High
NTP 1993 (mouse)	High	
Oral acute exposure		
Animal studies		
BASF Corp. 1990l (rat)	High	
BASF Corp. 1990m (rabbit)	High	
BASF Corp. 1991c (rat)	High	High
BASF Corp. 1991c (rabbit)	High	
Union Carbide Chem & Plas Co. 1991f (rat)	Low	
Union Carbide Chem & Plas Co. 1991o (rat)	Moderate	
Oral intermediate exposure		
Animal studies		
Union Carbide Chem & Plas Co. 1991w (mouse)	Moderate	
Union Carbide Chem & Plas Co. 1991r (rat)	Moderate	Moderate
Union Carbide Chem & Plas Co. 1991ee (dog)	Moderate	
Oral chronic exposure		
Animal studies		
van Miller et al. 2002 (rat)	High	High
Outcome: Dermal effects		

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
Dermal acute exposure		
Human studies		
Controlled exposure		
Union Carbide Corp. 1966 (irritation)	Low	Low
Union Carbide Corp. 1980 (irritation)	Low	
Animal studies		
Union Carbide Chem & Plas Co. 1991y (mouse)	Moderate	
Union Carbide Chem & Plas Co. 1991aa (rabbit)	Very low	
Union Carbide Corp. 1992a (rabbit)	Very low	Moderate
Union Carbide Corp. 1992b (rabbit)	Very low	
Union Carbide Corp. 1992c (rabbit)	Very low	
Union Carbide Corp. 1992h (rabbit)	Very low	
Dermal intermediate exposure		
Animal studies		
Werley et al. 1996 (rat)	High	High
Outcome: Ocular effects		
Ocular acute exposure (airborne vapor)		
Human studies		
Controlled exposure		
Cain et al. 2007	Moderate	Moderate
Animal studies		
Hoechst Celanese Corp. 1981 (rat)	Moderate	High
Union Carbide Corp. 1992e (rat)	High	
Ocular acute exposure (ocular instillation)		
Animal studies		
Union Carbide Chem & Plas Co. 1991cc (rabbit)	Moderate	
Union Carbide Corp. 1992h (rat)	Very low	
Union Carbide Corp. 1992a (rabbit)	Very low	Moderate
Union Carbide Corp. 1992b (rabbit)	Very low	
Union Carbide Corp. 1992c (rabbit)	Very low	

B.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that are considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, gastrointestinal, renal, dermal, and ocular effects are presented in Table B-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with glutaraldehyde exposure is presented in Table B-19.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables B-14, B-15, and B-16). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the end points to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Table B-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory Effects			
Cross-sectional cohort studies	Moderate	None	Moderate
Cohort studies	Moderate	-1 for risk of bias: studies in risk of bias second tier	Low
Human controlled exposure studies	Moderate	+1 for consistency: threshold levels were consistent across studies	High
Animal studies	High	None	High
Outcome: Gastrointestinal Effects			
Animal studies	High	None	High
Outcome: Renal Effects			
Animal studies	High	None	High
Outcome: Dermal Effects			
Human controlled exposure studies	Low	None	Low
Animal studies	High	None	High
Outcome: Ocular Effects			
Human controlled exposure studies	Moderate	None	Moderate
Animal studies	High	+1 consistency: effects were consistently observed	High

Table B-19. Confidence in the Body of Evidence for Glutaraldehyde

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	High	High
Gastrointestinal effects	No data	High
Renal effects	No data	High
Dermal effects	Low	High
Ocular effects	Moderate	High

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient

  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

B.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for glutaraldehyde, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence which was established in the sixth step of the systematic review (Section B.6) and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome

A summary of the level of evidence of health effects for glutaraldehyde is presented in Table B-20.

Table B-20. Level of Evidence of Health Effects for Glutaraldehyde

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	High	Health effect (inhalation only)	High
Gastrointestinal effects	No data	No data	No data
Renal effects	No data	No data	No data
Dermal effects	Low	Health effect (dermal contact)	Low
Ocular effects	Moderate	Health effect (ocular contact)	Moderate
Animal studies			
Respiratory effects	High	Health effect (inhalation only)	High
Gastrointestinal effects	High	Health effect (oral only)	High
Renal effects	High	Health effect (inhalation, oral)	High
Dermal effects	High	Health effect (dermal contact)	High
Ocular effects	High	Health effect (ocular contact)	High

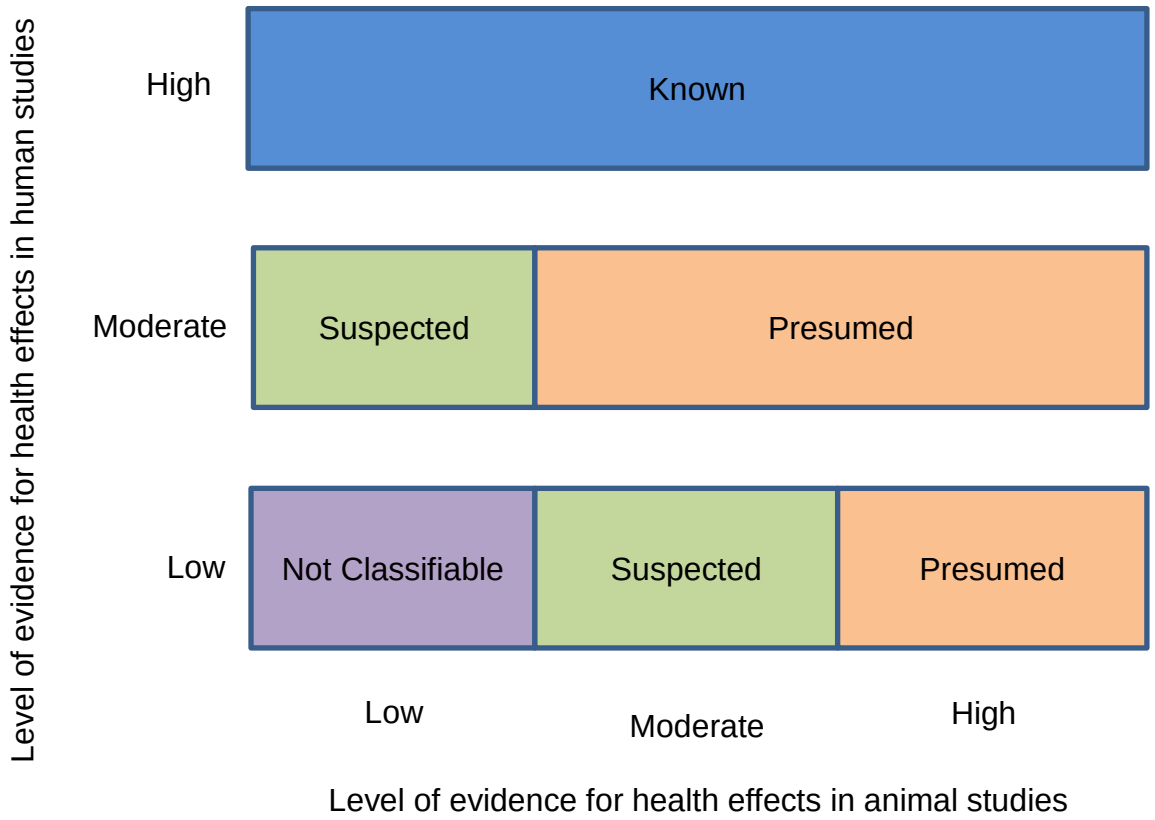
B.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure B-2 and described below.

Figure B-2. Hazard Identification Scheme



- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusions categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for glutaraldehyde are presented in Table B-21.

Table B-21. Hazard Identification Conclusions for Glutaraldehyde

Outcome	Hazard identification
Respiratory effects	Known health effect following inhalation exposure
Gastrointestinal effects	Presumed health effect following oral exposure
Renal effects	Presumed health effect
Dermal effects	Presumed health effect following dermal exposure
Ocular effects	Presumed health effect following ocular exposure

APPENDIX C. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.10, "Interactions with Other Substances," and Section 3.11, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page C-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

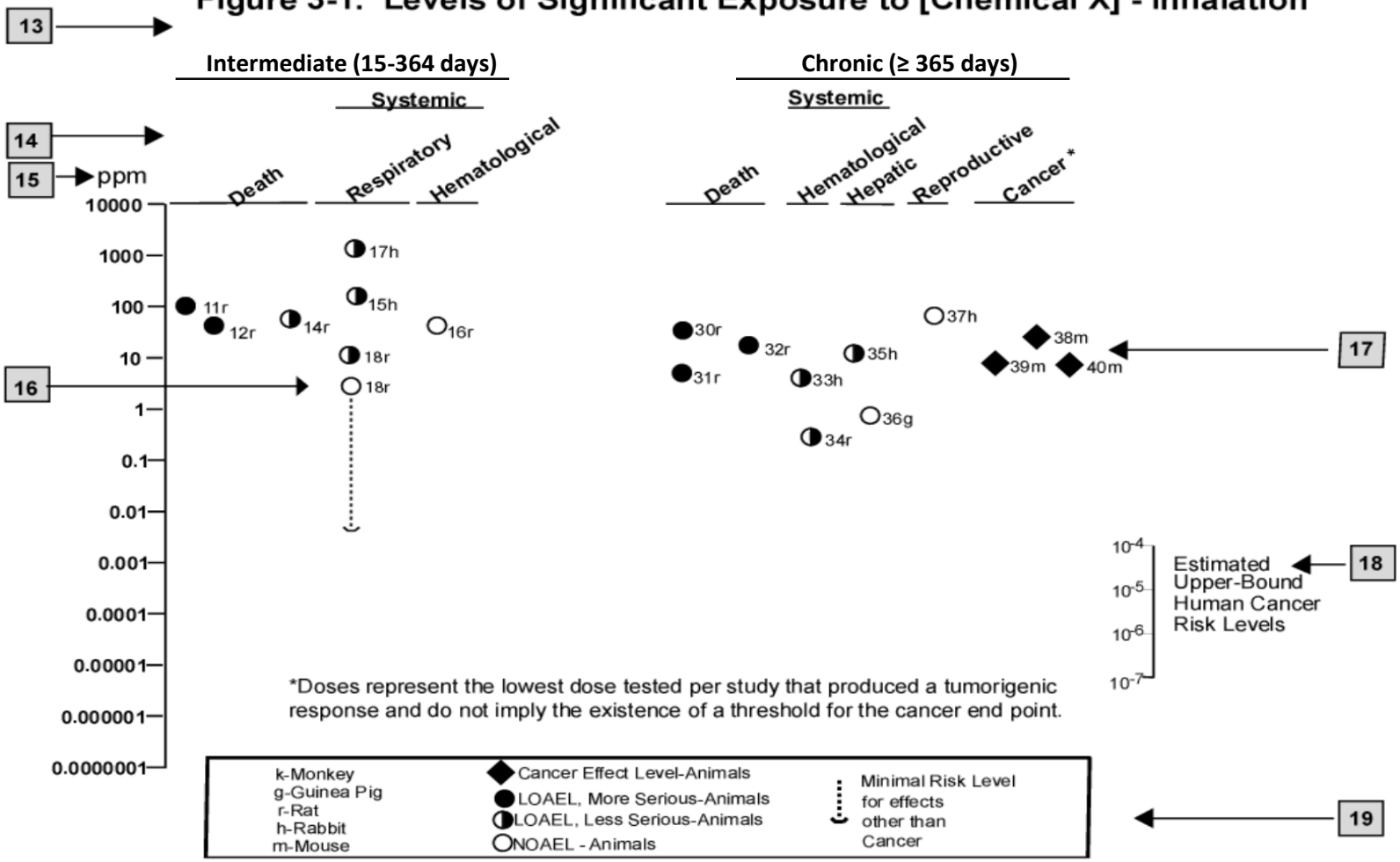
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BALF	bronchoalveolar lavage fluid
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMC_x	concentration that produces a X% change in response rate of an adverse effect
$BMCL_X$	95% lower confidence limit on the BMC_X
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid

DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/NA/IMDG	Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HEC	Human Equivalent Concentration
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill

m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA

OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound

WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result