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 (e.g., death, systemic, immunological, neurological, reproductive, developmental, 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				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 WI				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

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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 exposures 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)

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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	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

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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

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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

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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

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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

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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)

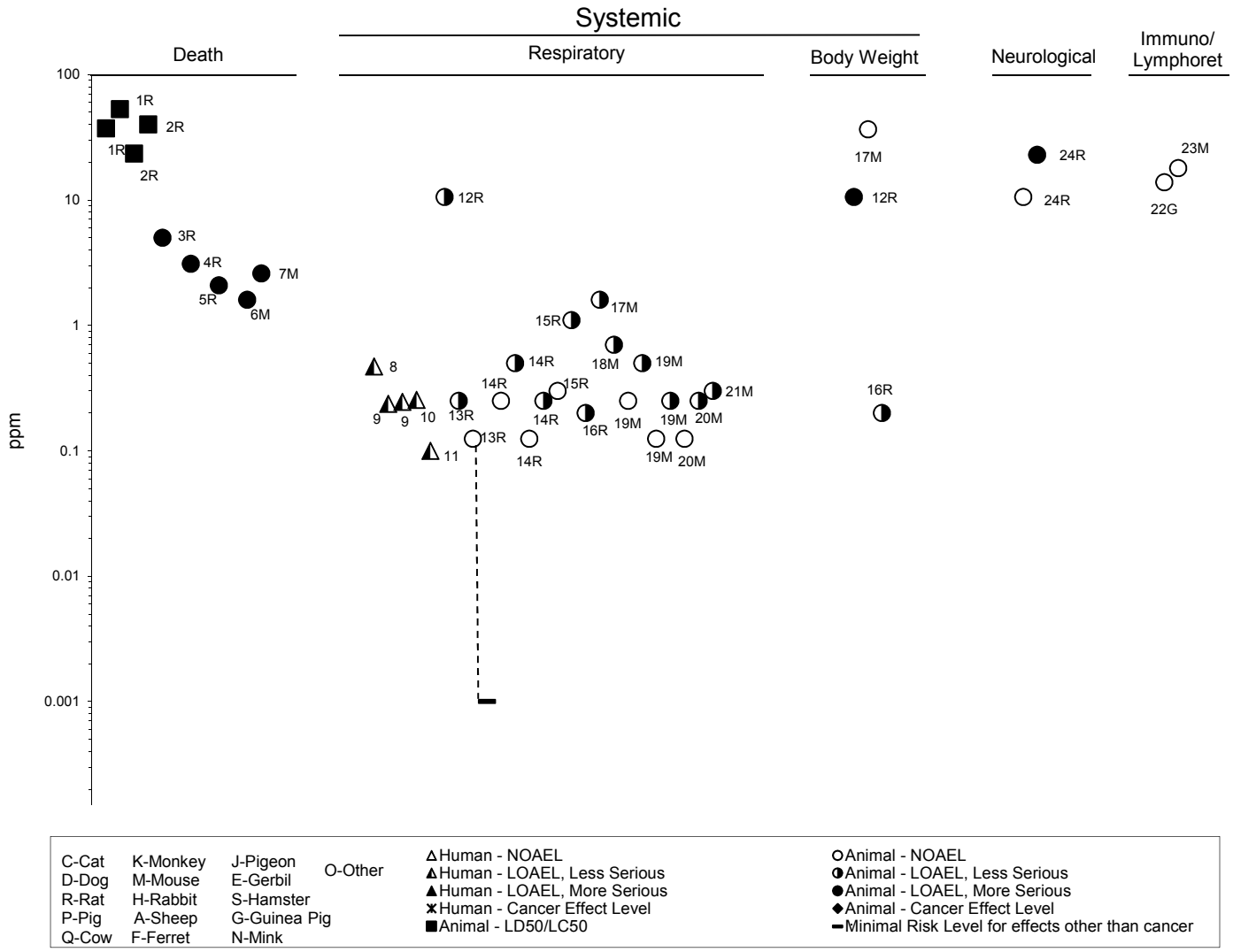


Figure 3-1. Levels of Significant Exposure to Glutaraldehyde - Inhalation *(Continued)*

Intermediate (15-364 days)

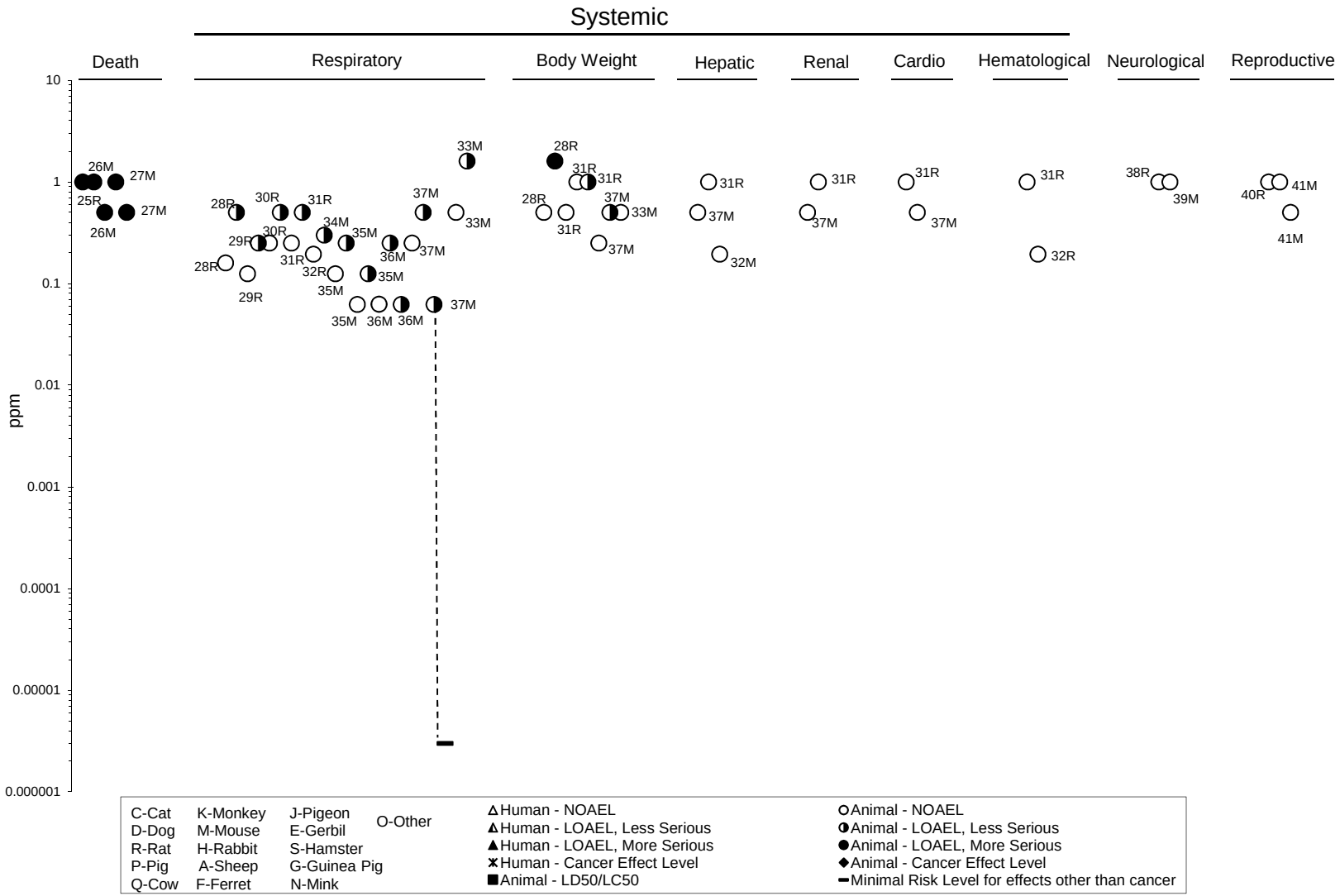


Figure 3-1. Levels of Significant Exposure to Glutaraldehyde - Inhalation *(Continued)*

Chronic (≥365 days)

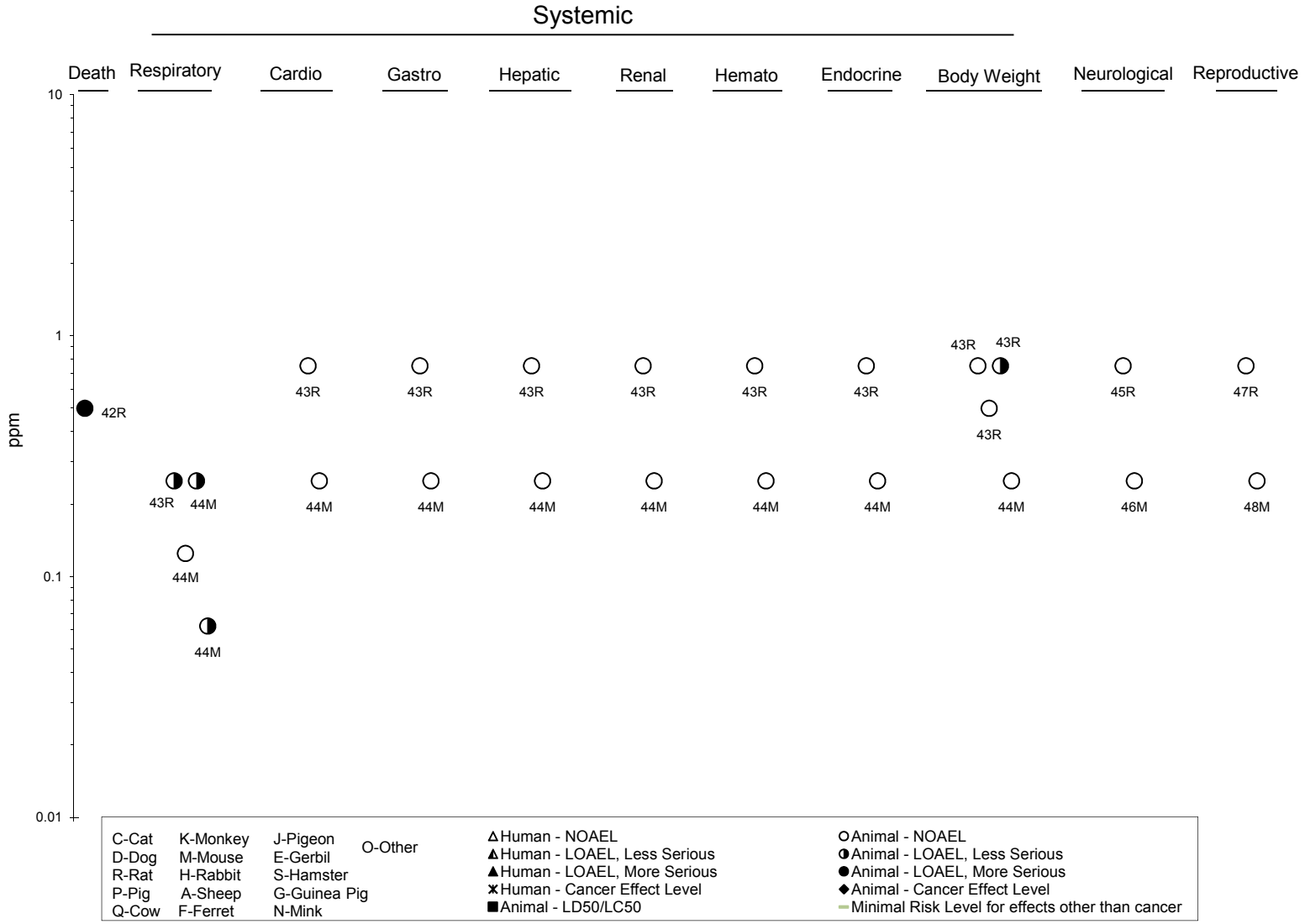


Table 3-2. Reported Respiratory Responses in Humans Exposed to Glutaraldehyde Vapor

Reference/subjects	Monitoring detail	Airborne concentration	Response
Union Carbide Corp. 1976 Controlled study: four female and five male volunteers exposed to 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 (e.g., irritation): 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 membranes, 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 (scales or flakes) 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

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
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]

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
13 Weeks	Squamous metaplasia	0/5	0/5	0/5	0/5	3/5 (0.8)	–[d]
	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

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 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

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)

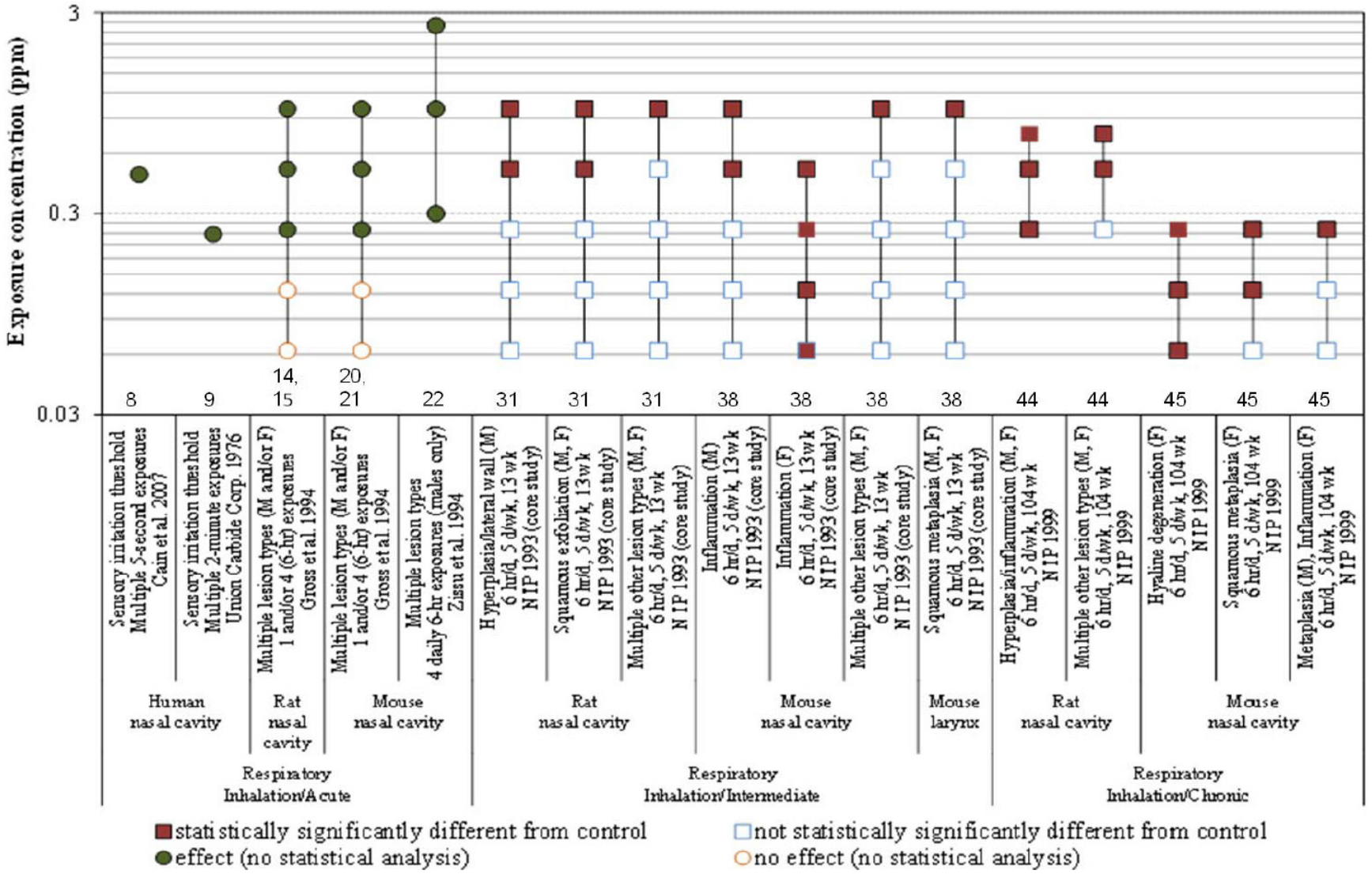
[a]Severity (in parentheses) is the average grade of lesions in affected animals where: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly increased relative to chamber control group by the Poly-3 test ($p \leq 0.05$).
[c]Significantly increased relative to chamber control group by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

Source: NTP 1999

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.

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.

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



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.

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 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

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				734	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				540	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				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				410	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				499	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				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				22.5	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	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	10 50 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	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			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		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)

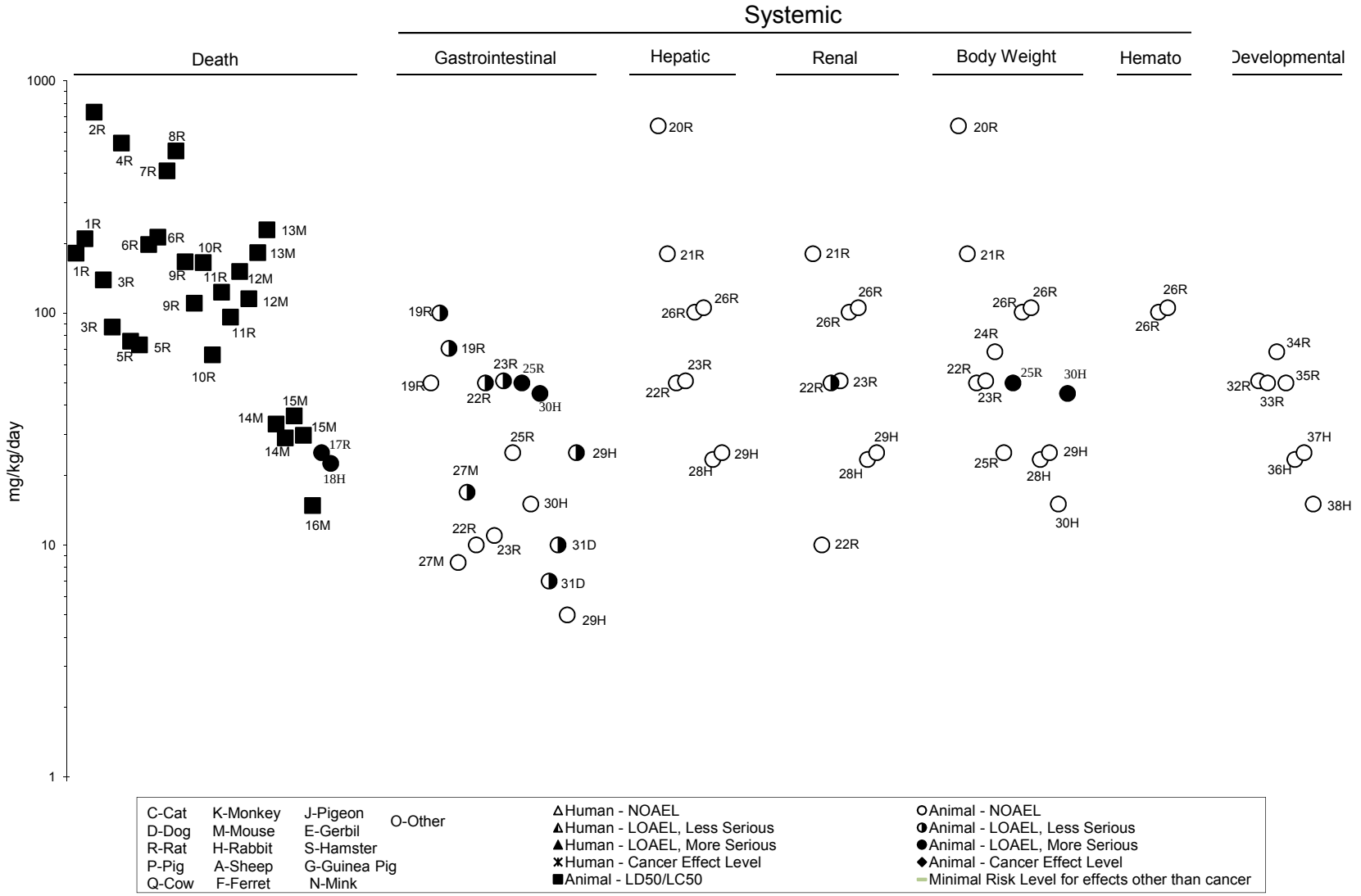


Figure 3-3. Levels of Significant Exposure to Glutaraldehyde - Oral *(Continued)*

Intermediate (15-364 days)

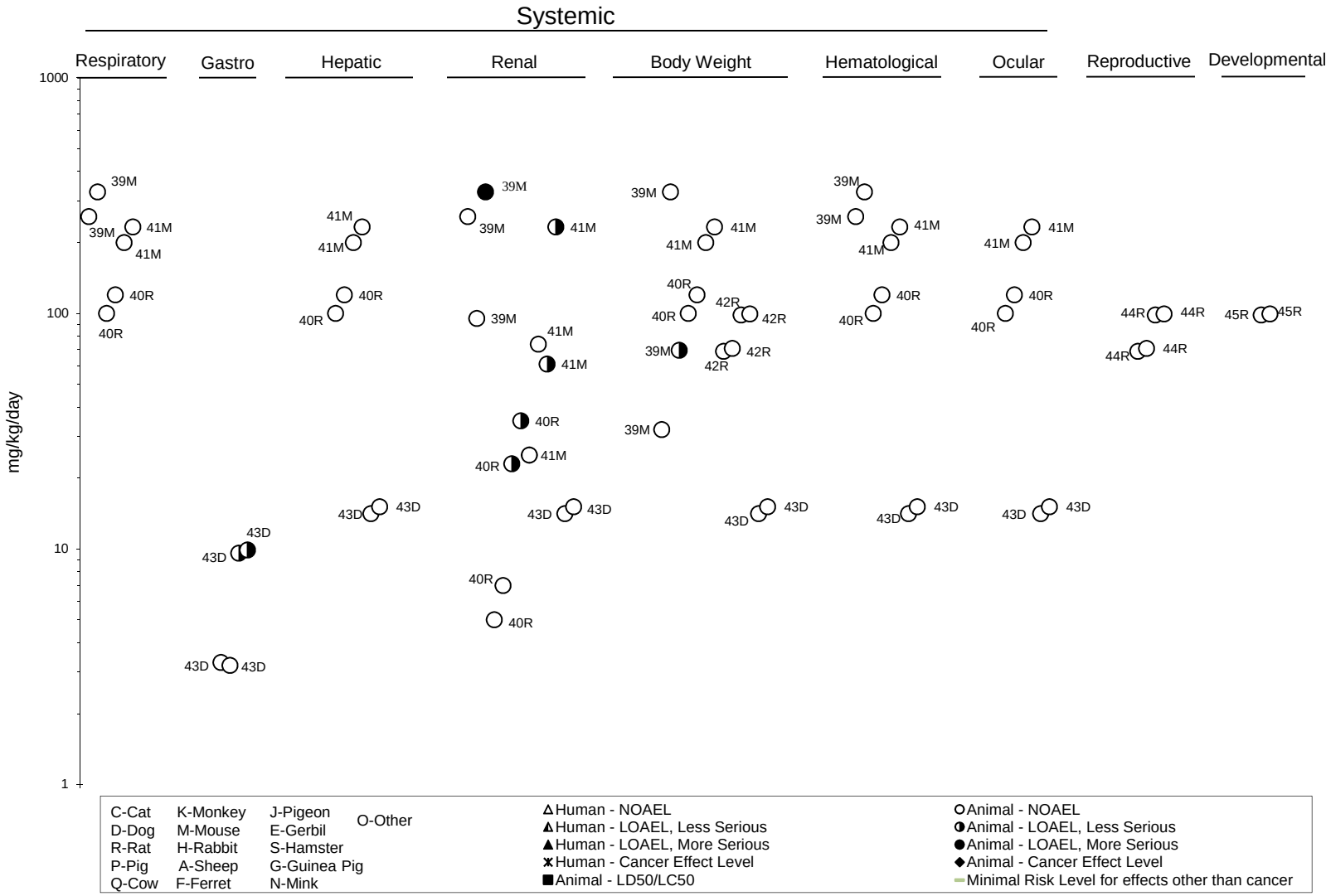
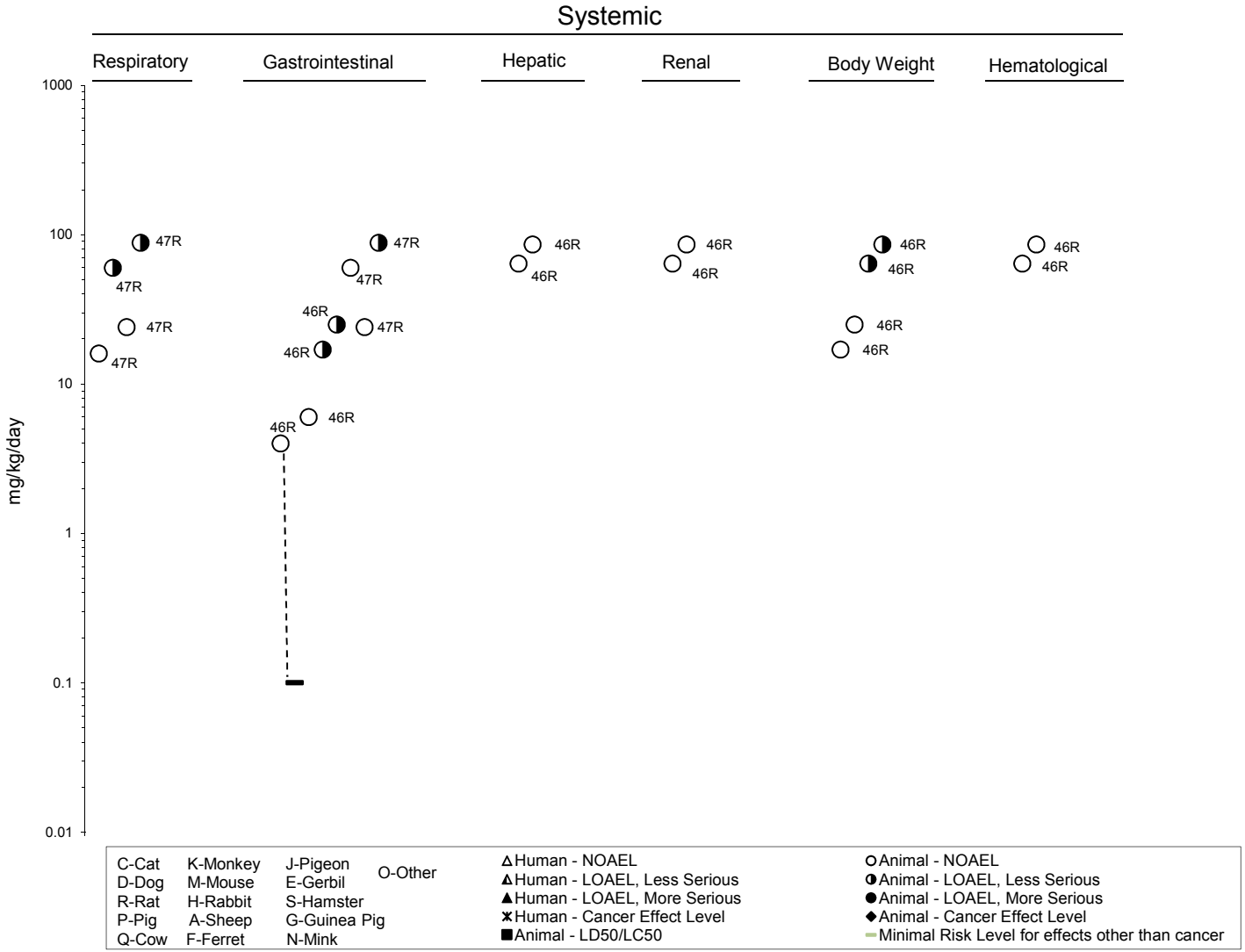


Figure 3-3. Levels of Significant Exposure to Glutaraldehyde - Oral *(Continued)*

Chronic (≥365 days)



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 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) was 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 (approximately 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 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

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 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

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 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,

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%)

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).

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

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
S. typhimurium TA2638	Gene mutation	No data	+	Levin et al. 1982

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

Species/test system	End point	Results		Reference
		With activation	Without activation	
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
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Union Carbide Chem & Plas Co. 1991jj

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	–	–	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

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 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 testicular DNA from 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. Variability 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 cytosolic, 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.

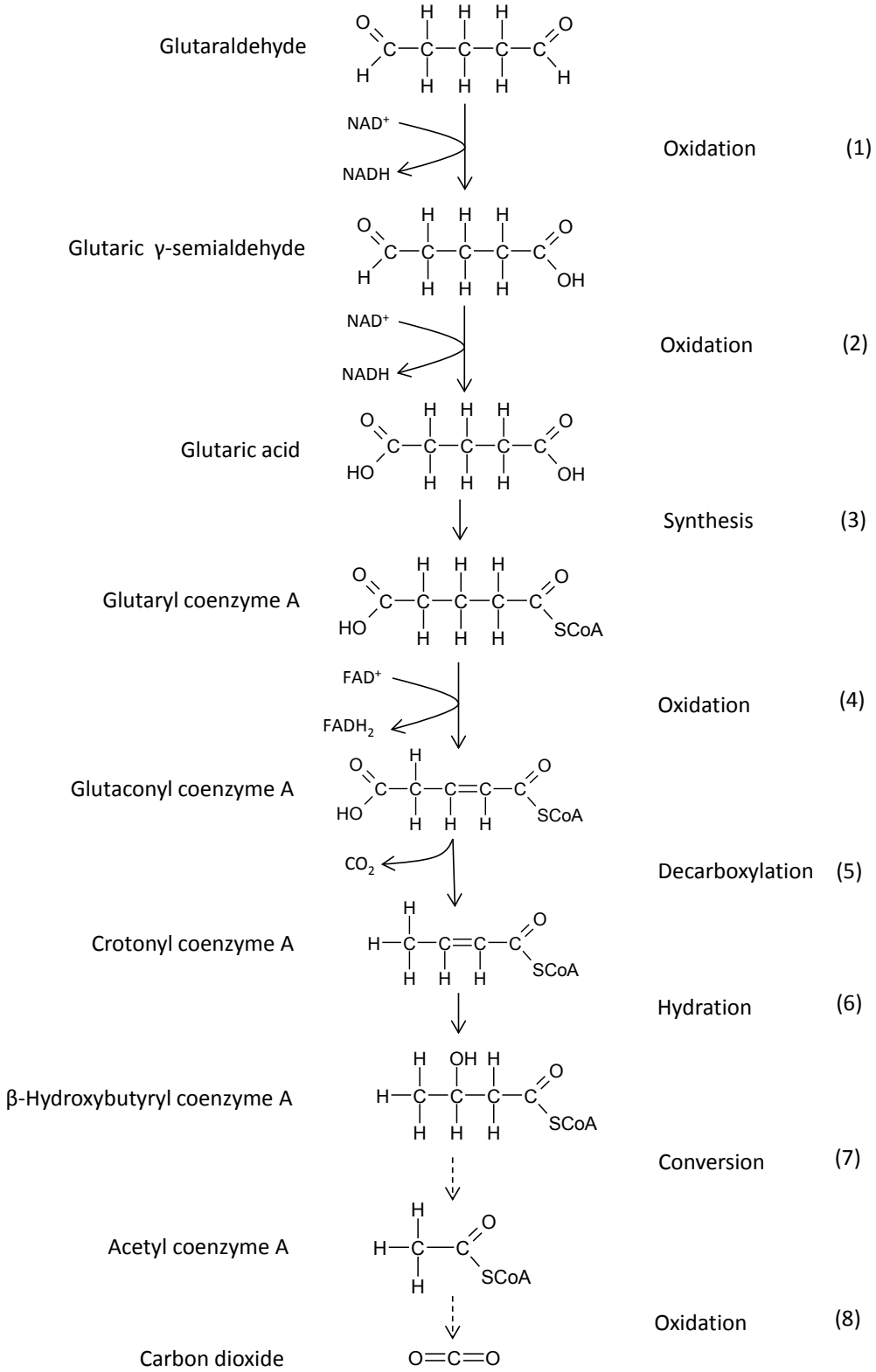
3.4.3 Metabolism

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

Figure 3-4. Proposed Metabolic Scheme for Glutaraldehyde



Source: Beauchamp et al. 1992

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.

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%, and 12–20% (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. However, if the uptake and disposition of the chemical substance(s) are adequately described, 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.

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

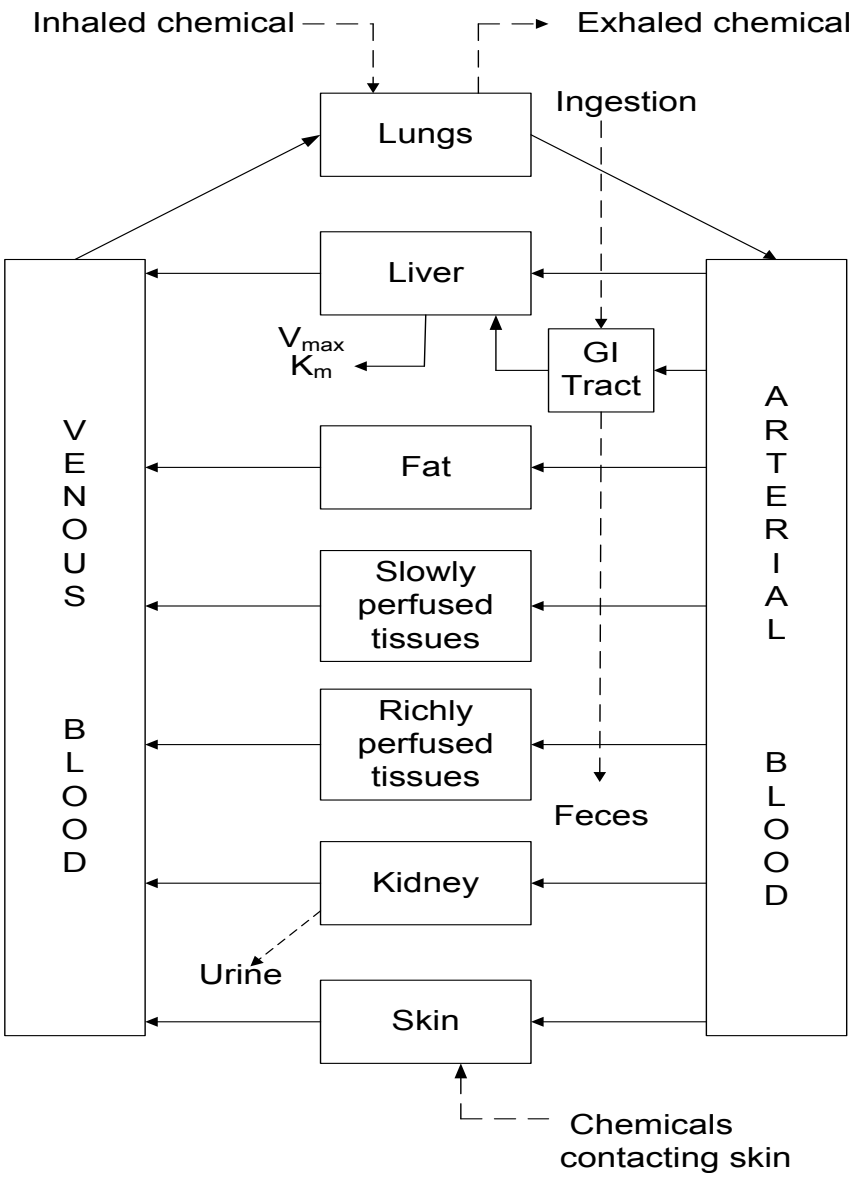
3.5.1 Pharmacokinetic Mechanisms

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,

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

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 (approximately 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 most 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 adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related 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 that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage 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). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is 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 brain, there are differences between fetuses/infants and adults that 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; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. 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 given their low glomerular filtration rate and not having 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 exposure to glutaraldehyde are discussed in Section 3.9.1.

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). Biomarkers of effects caused by glutaraldehyde are discussed in Section 3.9.2.

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. If biomarkers of susceptibility exist, they are discussed in Section 3.11, Populations That Are Unusually Susceptible.

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. Factors involved with increased susceptibility 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 will describe clinical practice and research concerning methods for reducing toxic effects of exposure to glutaraldehyde. 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, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to glutaraldehyde can be consulted for medical advice. The following texts provide specific information about treatment following exposures to glutaraldehyde:

Hoffman RS, Howland MA, Lewin NA, et al. 2015. Glutaraldehyde. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw-Hill Education, 1301-1302.

Leikin JB, Paloucek FP. 2008. Glutaraldehyde. In: Poisoning and toxicology handbook. 4th ed. Boca Raton, FL: CRC Press, 800.

NLM. 2017. National Library of Medicine. Environmental Health & Toxicology. https://sis.nlm.nih.gov/enviro.html. April 16, 2017

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

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 have been reported. 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 and in patients with central nervous system depression. Activated charcoal should not be administered due to risks associated with emesis as well as its ability to obscure findings should endoscopy become necessary.

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

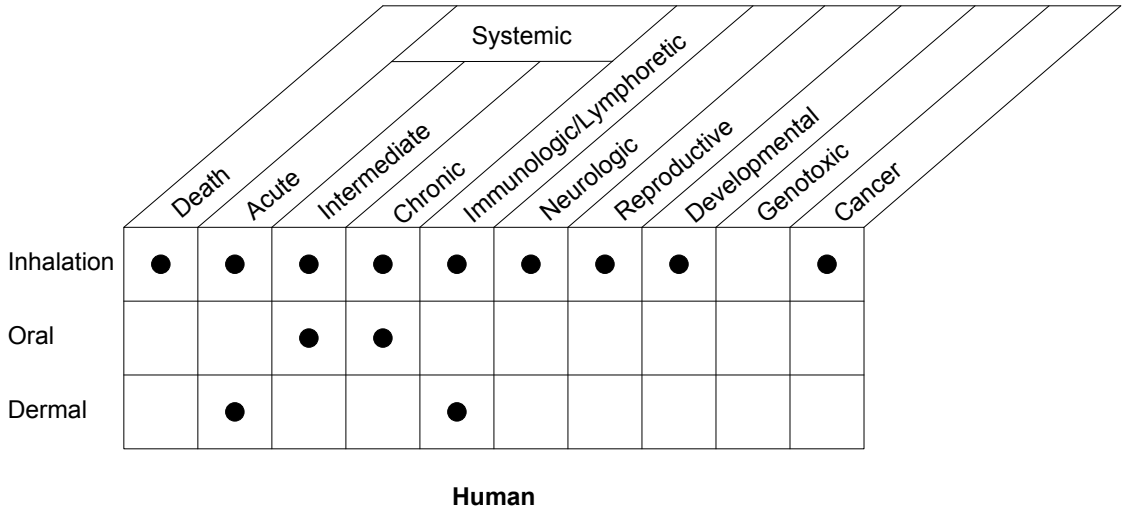
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glutaraldehyde is available. Where adequate information is 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 adverse 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 risk 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.

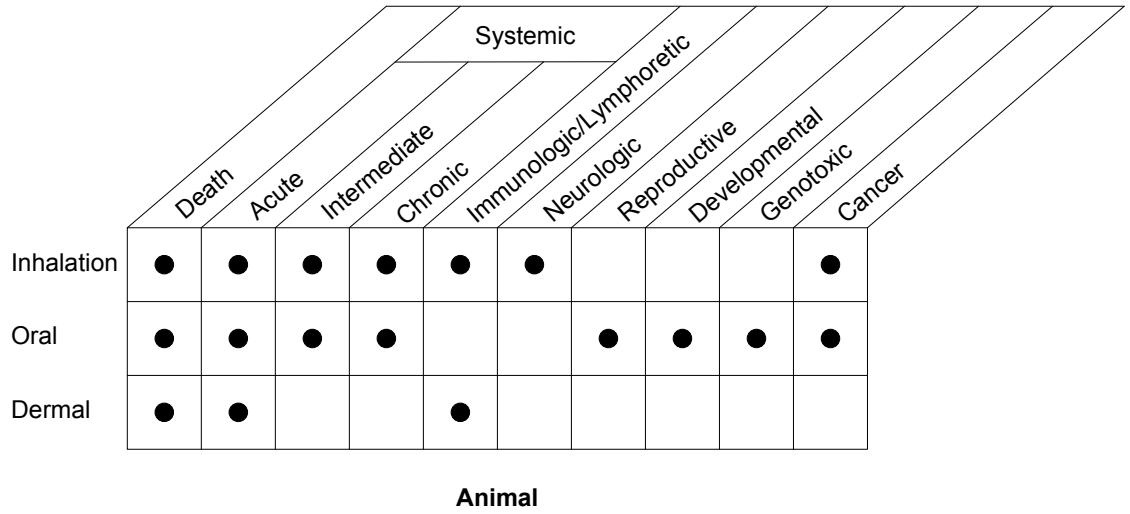
3.13.1 Existing Information on Health Effects of Glutaraldehyde

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

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



Human



Animal

● Existing Studies

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; 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).

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 hypersensitivity. 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).