APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: July 2017
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 0.001 [ ] mg/kg/day [x] ppm

References:

Gross EA, Mellick PW, Kari FW, et al. 1994. Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam Appl Toxicol 23(3):348-362.

NTP. 1993. NTP Technical report on toxicity studies of glutaraldehyde (CAS No. 111-30-8) administered by inhalation to F344/N tats and B6C3F1 mice. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. 25. NIH Publication 93-3348, Number 25.

The rat and mouse studies in the report of NTP (1993) are the same as the studies in the report of Gross et al. (1994). The report of Gross et al. (1994) provides a more detailed quantitative listing of glutaraldehyde-induced nasal lesions.

Experimental design: In a study designed to evaluate the time course of glutaraldehyde-induced nasal lesions, male and female F344 rats and B6C3F1 mice were exposed to glutaraldehyde vapor for 6 hours/day for 1 or 4 days, or 6 or 13 weeks at glutaraldehyde vapor concentrations of 0.0625, 0.125, 0.250, 0.5, or 1 ppm and sacrificed for evaluation of exposure-related nasal lesions.

Effect noted in study and corresponding doses: Exposure-related increased incidences of rats and mice exhibiting selected nasal lesions were observed following exposure to glutaraldehyde vapor at 0.250 ppm 6 hours per day for as little as 1 or 4 days; there were no apparent exposure-related effects on nasal lesion incidences at 0.125 ppm (Table A-1). This study identified a NOAEL of 0.125 ppm, and the lowest LOAEL (0.25 ppm for histopathological nasal lesions) among the acute-duration inhalation studies. Therefore, the principal study (Gross et al. 1994; NTP 1993) and the critical effect (glutaraldehyde-induced histopathological nasal lesions) serve as the basis for derivation of an acute-duration inhalation MRL for glutaraldehyde.

Table A-1. Incidences of Male and Female F344 Rats and B6C3F1 Mice with Selected Histopathologic Nasal Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day for 1 or 4 Days[a]

Species (gender)	Exposure level (ppm)	Squamous exfoliation		Intraepithelial neutrophils		Subepithelial neutrophils		Epithelial erosions	
		1 day	4 days	1 day	4 days	1 day	4 days	1 day	4 days
Rat (male)	0	0/5	0/5	0/5	0/5	0/5	1/5 (0.2)[b]	0/5	0/5
	0.0625	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/4	0/5	0/4	0/5	0/4	2/5 (0.4)	0/4	0/5
	0.250	1/5	0/5	1/5 (0.4)	0/5	3/5 (0.8)	1/5 (0.2)	1/5	1/5
	0.500	3/5	3/5	2/5 (0.4)	5/5 (1.4)	5/5 (1.8)	5/5 (1.6)	5/5	2/5
	1.00	5/5	5/5	5/5(1.2)	5/5 (2.6)	5/5 (2.6)	5/5 (3.4)		5/5
Rat (female)	0	0/5	0/5	0/5	1/5 (0.2)	0/5	2/5 (0.4)	0/5	0/5
	0.0625	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	0/5	0/5	1/5 (0.4)	0/5	1/5	0/5
	0.250	2/5	3/5	0/5	2/5 (0.4)	1/5 (0.2)	4/5 (1.4)	0/4	2/5
	0.500	3/5	5/5	2/5 (0.6)	5/5 (2.2)	5/5 (2.4)	5/5 (2.8)	4/5	3/5
	1.00	4/5	5/5	4/5 (1.0)	5/5 (3.4)	5/5 (2.8)	5/5 (3.8)		5/5
Mouse (male)	0	0/5	0/5	1/5 (0.2)	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.0625	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	1/5 (0.2)	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.250	0/5	4/5	0/5	1/5 (0.2)	1/5 (0.2)	2/5 (0.4)	0/5	0/5
	0.500	4/5	2/5	1/5 (0.2)	4/5 (1.8)	2/5 (0.4)	4/5 (1.8)	1/5	1/5
	1.00	5/5	5/5	5/5 (1.0)	5/5 (2.8)	5/5 (1.6)	5/5 (3.2)	2/5	2/5
Mouse (female)	0	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	0.0625	0/5	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5	0/5
	0.125	0/5	0/5	0/5	0/5	1/5 (0.2)	0/5	0/5	0/5
	0.250	0/5	2/5	0/5	1/5 (0.4)	0/5	1/5 (0.4)	0/5	0/5
	0.500	5/5	5/5	0/5	5/5 (1.0)	2/5 (0.4)	5/5 (1.6)	0/5	0/5
	1.00	4/5	5/5	1/5 (0.4)	4/5 (0.8)	3/5 (1.2)	5/5 (2.0)	1/5	2/5

[a]Gray shaded cells suggest a toxicologically significant increased incidence from controls.
[b]Severity (in parentheses) is the mean for all animals in a group where: 0 = no lesion; 1 = minimal; 2 = mild; 3 = moderate; and 4 = marked.

Sources: Gross et al. 1994; NTP 1993

Dose and end point used for MRL derivation: 0.125 ppm (adjusted for continuous exposure and converted to a human equivalent concentration resulting in a $NOAEL_{HEC}$ of 0.003 ppm); a LOAEL of 0.25 ppm for glutaraldehyde-induced nasal lesions was identified.

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL

[x] 1 for extrapolation from animals to humans using dosimetric conversion
[x] 3 for human variability

An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for human variability consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Derivation of a HEC based on the $NOAEL_{ADJ}$ was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde) using the following equation:

$RGDR_{ET} = (VE/SA_{ET})_A / (VE/SA_{ET})_H$ [equation 4-18 in EPA 1994]

where:

RGDR = ratio of the regional gas dose in animals to that of humans
VE = minute volume (cm^3/minute)
SA = surface area (cm^2)
$_{ET}$ = extrathoracic
$_A$ = animal
$_H$ = human

EPA-reported SA_{ET} values for rats (15 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). Minute volumes were taken from Table 1-4 of EPA (1988) in which they were presented as m^3/day (0.14 m^3/day = 97.2 cm^3/minute for subchronic exposure of the female F344 rat). Subchronic values were used because the rats were approximately 6–7 weeks old at the initiation of exposures. According to EPA (1994), the default minute volume for humans is 13,800 cm^3/minute. Therefore:

$RGDR_{ET}$ (rat) = (97.2 mL/minute/15 cm^2) / (13,800 mL/minute/200 cm^2) = 6.48/69 = 0.0939

The human equivalent NOAEL was calculated according to the following equation:

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RGDR_{ET}$ (rat) = 0.031 ppm x 0.0939 = 0.003 ppm ($3x10^{-3}$ ppm)

Was a conversion used from intermittent to continuous exposure? The 6-hour exposure was converted to a continuous exposure scenario by multiplying the 6-hour NOAEL of 0.125 ppm by 6 hours/24 hours, resulting in a $NOAEL_{ADJ}$ of 0.031 ppm. The adjustment to account for continuous exposure scenarios is necessary because nasal lesions were observed in glutaraldehyde-exposed rats and mice at lower exposure levels following 6 or 13 weeks of repeated 6-hour exposures than those eliciting nasal lesions following a single 6-hour exposure or repeated 6-hour exposures on 4 consecutive days.

Other additional studies or pertinent information that lend support to this MRL: In a study of Union Carbide Corp (1992d), rhinitis and mild atrophy of the olfactory mucosa were observed in male and female F344 rats exposed to glutaraldehyde vapor at 3.1 ppm for 6 hours/day for 9 exposures in 11 days; at an exposure level of 1.1 ppm, males (but not females) exhibited rhinitis and mild squamous metaplasia of the olfactory mucosa. This study identified a NOAEL of 0.3 ppm and a LOAEL of 1.1 ppm for nasal lesions in the male rats. Zissu et al. (1994) observed histopathological lesions in the respiratory epithelium of septum and naso- and maxilloturbinates of male Swiss OF1 mice exposed to glutaraldehyde vapor for 5 hours/day on 4 consecutive days at 0.3 ppm (the lowest concentration tested); the severity of glutaraldehyde-induced nasal lesions increased with increasing exposure concentration. This study did not identify a NOAEL.

Agency Contact (Chemical Manager): Susan Zells Ingber, A.B., M.S.P.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: July 2017
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 37
Species: Mouse

Minimal Risk Level: 0.00003 [ ] mg/kg/day [x] ppm

References:

Gross EA, Mellick PW, Kari FW, et al. 1994. Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam Appl Toxicol 23(3):348-362.

NTP. 1993. NTP Technical report on toxicity studies of glutaraldehyde (CAS No. 111-30-8) administered by inhalation to F344/N rats and B6C3F1 mice. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. 25. NIH Publication 93-3348, Number 25.

The rat and mouse studies in the report of NTP (1993) are the same as the studies in the report of Gross et al. (1994). The report of Gross et al. (1994) provides a more detailed quantitative listing of glutaraldehyde-induced nasal lesions.

Experimental design: Groups of male and female B6C3F1 mice (10/sex/group) were exposed to glutaraldehyde vapor for 6 hours/day, 5 days/week, for 13 weeks at concentrations of 0, 0.0625, 0.125, 0.25, 0.5, or 1.0 ppm and evaluated for survival, clinical signs, body weight, selected organ and tissue weights, and gross and histopathology (particularly the nasal cavity).

Effect noted in study and corresponding doses: Concentration-related increased incidence and severity of clinical signs of respiratory irritation and histopathologic nasal lesions (exfoliation, inflammation, hyperplasia, and ulceration of nasal squamous epithelium; granulocytes and necrosis in nasal passages; laryngeal squamous metaplasia; necrosis in nasal nares) were reported. Histopathologic nasal lesions were sometimes noted at exposure levels lower than those resulting in overt clinical signs of respiratory tract irritation. In general, glutaraldehyde-induced histopathologic respiratory tract lesions were confined to the anterior nasal cavity and were not observed in lower respiratory tract regions. Incidence data for selected nonneoplastic nasal lesions in the male and female B6C3F1 mice are presented in Table A-2. The incidence data for inflammation in the nasal vestibule/anterior nares of the B6C3F1 female mice from the core study (NTP 1993) were selected to serve as the basis for deriving an intermediate-duration inhalation MRL for glutaraldehyde because this lesion exhibited the lowest effect level (0.0625 ppm). All dichotomous models in the BMDS (Version 2.2) were fit to the incidence data for inflammation in the nasal vestibule/anterior nares of the female mice; the highest exposure group was dropped because the incidence of inflammation in this group was not reported (the study authors stated that "inflammation was a component of 'squamous exfoliation' and not diagnosed separately when the latter was present"). A BMR of 10% extra risk was applied. The results of the BMD analysis are summarized in Table A-3.

Table A-2. Incidences of Male and Female B6C3F1 Mice Exhibiting Selected Histopathologic Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks in the Core Study of NTP (1993)[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Males						
Nasal passages/turbinates						
Respiratory epithelium						
Inflammation	0	0	0	0	0	4(1.0)[b]
Squamous metaplasia	0	0	0	0	0	1 (1.2)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1 (1.0)	2 (1.0)	9 (2.8)[c]
Inflammation	0	0	0	0	7 (1.1)[c]	0[d]
Erosion	0	0	0	1 (1.0)	1 (1.0)	0
Larynx						
Squamous metaplasia	0	0	0	0	0	7 (1.6)[c]
Necrosis	0	0	0	0	0	2 (1.0)
Females						
Nasal passages/turbinates						
Respiratory epithelium						
Inflammation	0	0	0	0	1 (1.0)	7 (1.4) [c]
Squamous metaplasia	0	0	0	0	0	3 (1.0)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1 (1.0)	2 (2.5)	10 (2.8)[c]
Inflammation[e]	0	5 (1.0)[b]	8 (2.0)[c]	8 (1.6)[c]	8 (2.5)[c]	0[d]
Erosion	0	0	1 (1.0)	0	0	0
Larynx						
Squamous metaplasia	0	0	0	0	0	10 (1.6)[c]
Necrosis	0	0	0	0	0	2 (1.0)

[a]Incidence is the number of core-study animals with lesions for groups of 10 animals. Average severity (in parentheses) is based on the number of animals with lesions: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).
[d]Inflammation was a component of "squamous exfoliation" and not diagnosed separately when the latter was present.
[e]Gray-shaded cells depict the lesion incidence data that were subjected to benchmark dose (BMD) analysis.

Source: NTP 1993

Table A-3. Results from BMD Analysis of Incidences of Female B6C3F1 Mice Exhibiting Inflammation in the Nasal Vestibular/Anterior Nares Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks

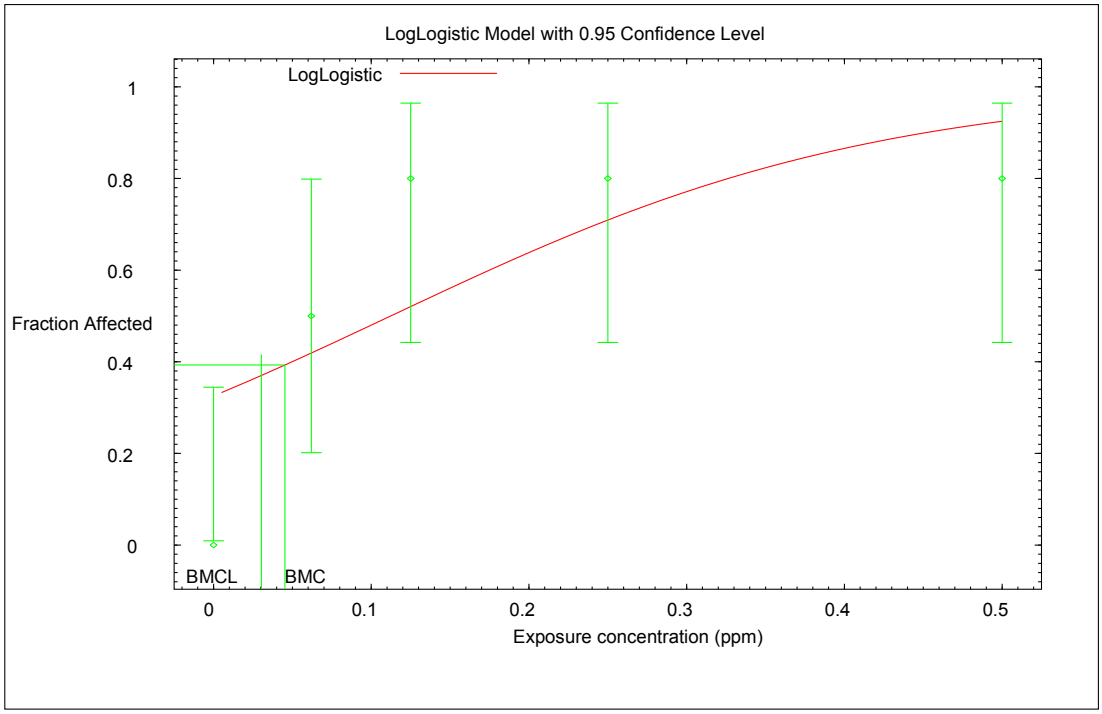
Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Logistic	3	10.88	0.01	-2.20	0.52	-2.20	61.44		
LogLogistic[d,e]	**4**	**1.63**	**0.80**	**0.00**	**-0.09**	**-0.98**	**47.40**	**0.0065**	**0.0034**
LogProbit[d]	4	8.81	0.07	0.00	0.85	-2.60	51.54		
Multistage (1-degree)[f]	4	10.75	0.03	0.00	0.12	-2.67	53.34		
Multistage (2-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Multistage (3-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Multistage (4-degree)[f]	4	10.75	0.03	0.00	1.12	-2.67	53.34		
Probit	3	10.99	0.01	-2.26	0.50	-2.26	61.92		
Weibull[c]	4	10.75	0.03	0.00	1.12	-2.67	53.34		

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The LogLogistic model was the only model providing adequate fit to the data.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; DF = degree of freedom

The Gamma, Logistic, LogProbit, Multistage, Probit, and Weibull models failed to meet conventional goodness-of-fit criteria because their χ^2 p-values were <0.1. The LogLogistic model provided adequate fit to the data (χ^2 p-value = 0.80, largest scaled residual -0.98), a BMC_{10} of 0.0065 ppm, and a $BMCL_{10}$ of 0.0034 ppm. Figure A-1 plots predicted incidences of the female mice exhibiting inflammation in the nasal vestibule/nares from the LogLogistic model and observed incidence values from data in Table A-3.

Figure A-1. Predicted and Observed Incidence of Female B6C3F1 Mice Exhibiting Inflammation in the Nasal Vestibular/Anterior Nares Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks.*



*BMC and BMCL are associated with a 10% extra risk change from control

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.0034 ppm, based on inflammation in the nasal vestibular/anterior nares of female B6C3F1 mice inhaling glutaraldehyde vapor.

[ ] NOAEL [ ] LOAEL [x] BMD Analysis

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 1 for extrapolation from animals to humans using dosimetric conversion
[x] 3 for human variability

An uncertainty factor of 1 (rather than the default 10) for extrapolation from animals to humans is justified because: (1) the dosimetric adjustment accounts for differences between rats and humans regarding respiratory tract kinetics, and (2) the critical effect (nasal irritation) is the result of the propensity of glutaraldehyde to react with and cross-link cell membrane proteins (Peters and Richards 1977), a mechanism of action common to laboratory animals and humans. The uncertainty factor for human variability consists of a pharmacokinetic contribution (default of 3) and a pharmacodynamic contribution (default of 3). The propensity of glutaraldehyde to react with and cross-link cell membrane proteins at the portal of entry is not expected to vary significantly. The critical effect (nasal lesions) is independent of glutaraldehyde absorption, distribution, metabolism, and elimination kinetics. Therefore, an uncertainty factor of 1 for intraspecies pharmacokinetics is justified. A default uncertainty factor of 3 for intraspecies pharmacodynamics is retained in the absence of empirical data to suggest otherwise.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Derivation of a human equivalent concentration (HEC) based on the $BMCL_{ADJ}$ was performed according to EPA (1994) cross-species dosimetric methodology for a category 1 gas where inhalation exposure-related effects occur within the extrathoracic region of the respiratory tract (the nasal cavity in the case of glutaraldehyde) using the following equation:

$RGDR_{ET} = (VE/SA_{ET})_A / (VE/SA_{ET})_H$ [equation 4-18 in EPA 1994]

where:

RGDR = ratio of the regional gas dose in animals to that of humans
VE = minute volume (cm^3/minute)
SA = surface area (cm^2)
$_{ET}$ = extrathoracic
$_A$ = animal
$_H$ = human

EPA-reported SA_{ET} values for mice (3 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). Minute volumes were taken from Table 1-4 of EPA (1988) in which they were presented as m^3/day (0.04 m^3/day = 27.8 cm^3/minute for subchronic exposure of the female B6C3F1 mouse). According to EPA (1994), the default minute volume for humans is 13,800 cm^3/minute. Therefore:

$RGDR_{ET}$ (mouse) = (27.8 mL/minutes/3 cm^2) / (13,800 mL/minutes/200 cm^2) = 9.27/69 = 0.134

The human equivalent $BMCL_{10}$ was calculated according to the following equation:

$BMCL_{10HEC} = BMCL_{10ADJ}$ x $RGDR_{ET}$ (mouse) = 0.0006 ppm x 0.134 = 0.00008 ppm ($8x10^{-5}$ ppm)

Was a conversion used from intermittent to continuous exposure? The 6-hour/day, 5 days/week exposure was converted to a continuous exposure scenario by multiplying the $BMCL_{10}$ of 0.0034 ppm by 6 hours/24 hours and 5 days/7 days, resulting in a $BMCL_{10ADJ}$ of 0.0006 ppm.

The adjustment to account for continuous exposure scenarios is necessary because nasal lesions were observed in glutaraldehyde-exposed rats and mice at lower exposure levels following 6 or 13 weeks of repeated 6-hour exposures than those eliciting nasal lesions following a single 6-hour exposure or repeated 6-hour exposures on 4 consecutive days.

Other additional studies or pertinent information that lend support to this MRL: The principal study (Gross et al. 1994; NTP 1993) included groups of male and female F344/N rats exposed to glutaraldehyde vapor for 6 hours/day, 5 days/week, for 13 weeks at 0.0625, 0.125, 0.250, 0.5, or 1 ppm as well. Nasal lesions similar to those observed in the mice were also noted in the rats (see Table A-4). In a similarly-designed histopathology time-course study that evaluated the progression of nasal lesions for up to 13 weeks (5/species/sex/exposure group/time point) (Gross et al. 1994; NTP 1993), neutrophilic infiltration into intra- and subepithelial regions of the nasal vestibule of female mice was identified as the most sensitive effect and was observed at the lowest exposure level tested (0.0625 ppm) (see Table A-5). The neutrophilic infiltration was consistent with inflammation in the core study, thus providing support to the findings of the core study.

Table A-4. Incidences of Male and Female F344/N Rats Exhibiting Selected Histopathologic Nasal Lesions Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week for 13 Weeks in the Core Study of NTP (1993)[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Males						
Respiratory epithelium						
Nasoturbinates/septum						
Hyperplasia	0	0	0	0	0	7 (1.7)[b]
Hyperplasia, goblet cell	0	0	0	1 (1.0)	3 (1.0)	9 (1.4)[b]
Squamous metaplasia	0	0	0	0	0	5 (2.0)[c]
Inflammation	0	0	0	0	0	7 (1.0)[b]
Lateral wall						
Hyperplasia	0	0	1 (1.0)	0	4 (1.0)[c]	7 (1.7)[b]
Squamous metaplasia	0	0	0	0	1 (1.0)	7 (2.5)[b]
Olfactory epithelium						
Degeneration	0	0	0	0	0	1 (2.0)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	1(1.0)	4 (1.0)[c]	9 (1.1)[b]
Inflammation	0	1 (1.0)	0	0	0	3 (1.0)
Females						
Respiratory epithelium						
Nasoturbinates/septum						
Hyperplasia	0	0	0	0	0	4 (1.7)[c]
Hyperplasia, goblet cell	0	0	0	0	0	8 (1.2)[b]
Squamous metaplasia	0	0	0	0	0	5 (1.4)[c]
Inflammation	0	0	0	1 (1.0)	0	5 (1.2)[c]
Lateral wall						
Hyperplasia	0	0	0	1 (2.0)	2 (1.0)	8 (1.6)[b]
Squamous metaplasia	0	0	0	1 (3.0)	0	8 (2.0)[b]
Olfactory epithelium						
Degeneration	0	0	0	0	0	2 (1.5)
Nasal vestibule/anterior nares						
Squamous exfoliation	0	0	0	3 (1.3)	7 (1.1)[b]	9 (1.7)[b]
Inflammation	1 (1.0)	0	0	0	0	0
Erosion	0	0	0	0	1 (1.0)	2 (2.0)

[a]Incidence is the number of core-study animals with lesions for groups of 10 animals. Average severity (in parentheses) is based on the number of animals with lesions: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).

Source: NTP 1993

Table A-5. Incidences of Male and Female F344/N Rats and B6C3F1 Mice Exhibiting Selected Histopathologic Lesions in the Nasal Vestibule Following Exposure to Glutaraldehyde Vapor 6 Hours/Day, 5 Days/Week For 13 Weeks in the Histopathology Time-Course Study[a]

	Exposure level (ppm)					
	0	0.0625	0.125	0.250	0.500	1.000
Male rat						
Squamous exfoliation	0	0	0	2	2	2
Intraepithelial neutrophils	5 (1.2)[b]	3 (0.8)	5 (1.0)	5 (1.2)	4 (1.2)	5 (1.6)
Subepithelial neutrophils	5 (1.0)	4 (1.0)	5 (1.2)	5 (1.6)	5 (1.4)	5 (2.0)
Epithelial erosions	1	1	0	1	1	1
Squamous metaplasia	1 (0.2)	0	0	0	5 (2.0)	5 (3.0)
Female rat						
Squamous exfoliation	0	0	0	0	2	4
Intraepithelial neutrophils	1 (0.2)	0	1 (0.4)	3 (1.0)	2 (0.8)	4 (1.4)
Subepithelial neutrophils	2 (0.4)	0	1 (0.8)	3 (1.0)	4 (1.8)	4 (2.0)
Epithelial erosions	0	0	0	0	0	1
Squamous metaplasia	0	0	0	0	3 (1.2)	5 (2.6)
Male mouse						
Squamous exfoliation	0	0	0	3	1	–[c]
Intraepithelial neutrophils	0	0	1 (0.2)	4 (1.6)	5 (2.6)	–
Subepithelial neutrophils	0	1 (0.2)	2 (0.8)	5 (2.2)	5 (2.8)	–
Epithelial erosions	0	0	0	1	3	–
Squamous metaplasia	0	0	0	0	1 (0.2)	–
Female mouse						
Squamous exfoliation	0	0	0	0	1/4	–
Intraepithelial neutrophils	0	4 (2.0)	5 (2.4)	5 (3.2)	4/4 (2.8)	–
Subepithelial neutrophils	2 (0.4)	5 (2.0	5 (2.8)	5 (3.2)	4/4 (2.8)	–
Epithelial erosions	0	0	0	0	0/4	–
Squamous metaplasia	0	0	0	0	1/4 (0.5)	–

[a]Gray shaded cells suggest a toxicologically significant increased incidence from controls.
[b]Incidence is the number of animals with lesions for groups of five animals unless a denominator is given. Severity (in parentheses) was averaged for five animals/group where: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.
[c]Not evaluated, all animals died.

Sources: Gross et al. 1994; NTP 1993

Agency Contact (Chemical Manager): Susan Zells Ingber, A.B., M.S.P.P.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Glutaraldehyde
CAS Numbers: 111-30-8
Date: July 2017
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 46
Species: Rat

Minimal Risk Level: 0.1 [x] mg/kg/day [ ] ppm

Reference: van Miller JP, Hermansky SJ, Losco PE, et al. 2002. Chronic toxicity and oncogenicity study with glutaraldehyde dosed in the drinking water of Fischer 344 rats. Toxicology 175(1-3):177-189.

Experimental design: In a 2-year chronic toxicity and oncogenicity study, Fischer 344 rats (100/sex/group) were administered glutaraldehyde (50.0–51.3% w/w aqueous solution) in the drinking water at concentrations of 0, 50, 250, or 1,000 ppm for 52 weeks (first interim sacrifice of 10/sex/group), 78 weeks (second interim sacrifice of 10/sex/group), or up to 104 weeks (main group). Author-reported average glutaraldehyde doses were 0, 4, 17, and 64 mg/kg/day, respectively, for the males and 0, 6, 25, and 86 mg/kg/day, respectively, for the females. Animals were observed for survival, clinical signs, body weight, and food and water consumption. Eyes were examined by indirect ophthalmoscopy before the start of dosing and after weeks 52, 78, and 104. Hematology and serum chemistry evaluations were performed at weeks 12, 26, 52, 78, and 104 (10 rats/sex/group). Urine was collected from 10 rats/sex/ group during weeks 12, 25, 51, 77, and 103 for urinalysis. All surviving rats were sacrificed at week 104. At sacrifice, liver, kidneys, brain, heart, adrenal glands, and testes were removed and weighed. Comprehensive gross and histopathologic examinations were performed on all animals.

Effect noted in study and corresponding doses: Treatment-related effects included slightly depressed body weight and lesions of the stomach. The depressions in body weight were typically <10% in magnitude. Gross pathology revealed gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa) in 250- and 1,000-ppm male and female rats at 52-, 78-, and 104-week sacrifice (prevalences of 30, 10–20, and 10%, respectively) and in animals that died prior to scheduled sacrifice (prevalence of 40%). Histopathology revealed significantly increased incidences of 1,000-ppm male and female rats with mucosal hyperplasia in the stomach at terminal sacrifice (males: 7/51 versus 1/56 controls; females 7/56 versus 1/62 controls), but not at 52- or 78-week interim sacrifices. Incidences of this lesion at the lower dose levels were not significantly different from those of controls. This study identified NOAELs of 4 and 6 mg/kg/day for the male and female rats, respectively, and LOAELs of 17 and 25 mg/kg/day for male and female rats, respectively, for gastric irritation (multifocal color change, mucosal thickening, nodules, and ulceration affecting primarily the nonglandular mucosa).

Dose and end point used for MRL derivation: 4 mg/kg/day

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans

[x] 3 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Wistar rats (50/sex/group) were administered glutaraldehyde (50.5% active ingredient) in the drinking water for up to 24 months at concentrations of 0, 100, 500, or 2,000 ppm (approximate daily glutaraldehyde intakes of 0, 3, 16, and 60 mg/kg/day, respectively, for the males and 0, 5, 24, and 88 mg/kg/day, respectively, for the females) (BASF 2013; Confidential 2002). Increased incidences of non-neoplastic lesions were observed at the 2,000 ppm exposure level and involved the larynx (squamous metaplasia in males [18/50 versus 0/50 controls] and females [30/50 versus 0/50 controls]) and trachea (squamous metaplasia in males [4/50 versus 0/50 controls] and females [11/50 versus 0/50 controls]). In addition, significant trends for increasing incidence with increasing glutaraldehyde concentration were noted for diffuse metaplasia in the larynx of male and female rats, focal metaplasia in the larynx of females, focal squamous metaplasia in the trachea of males and females, and diffuse metaplasia in the trachea of females. Metaplasia was nearly always accompanied by accumulation of keratin detritus in the laryngeal and/or tracheal lumen. Some high-dose rats with laryngeal/tracheal metaplasia also exhibited foreign body granulomas in the lung and/or inflammation in the tracheal lumen. Significantly increased incidence of erosion/ulceration was noted in the glandular stomach of 2,000-ppm females. Purulent inflammation in the nasal cavity was seen in three males and six females of the highest exposure level.

Agency Contact (Chemical Manager): Susan Zells Ingber, A.B., M.S.P.P.

This page is intentionally blank.

APPENDIX B. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR GLUTARALDEHYDE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to glutaraldehyde, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013a; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to glutaraldehyde:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

B.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to glutaraldehyde. The inclusion criteria used to identify relevant studies examining the health effects of glutaraldehyde are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

B.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of glutaraldehyde. Studies for other sections of the toxicological profile were also identified in the literature search and screen step. Although these studies were not included in the systematic review process, the results of some studies (e.g., mechanistic studies, toxicokinetic studies) were considered in the final steps of the systematic review. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of glutaraldehyde have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.

APPENDIX B

Table B-1. Inclusion Criteria for the Literature Search and Screen

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Cancer

B.2.1 Literature Search

The following databases were searched, without date restrictions, in January 2013:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER
- National Pesticide Information Retrieval System (NPIRS)
- Toxic Substances Control Act Test Submissions (TSCATS) and TSCATS2

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

The search strategy used the chemical name, CAS number (i.e., 111-30-8), synonyms, and Medical Subject Headings (MeSH) terms for glutaraldehyde. A total of 5,197 records were identified and imported into EndNote (version 5). After the identification and removal of 1,850 duplicates by EndNote, the remaining 3,337 records were moved to the literature screening step.

An update literature search was conducted in November 2016 of the PubMed, TOXLINE, TOXCENTER, NPIRS, NTP, and TSCATS/TSCATS2 databases utilizing the same search strategy as the January 2013 literature search. The update search identified 2,107 records; 376 records were duplicates of records from the 2013 search and were excluded. A total of 1,731 records were imported into EndNote (version X7). After the identification and removal of an additional 150 duplicates by Endnote, the remaining 1,581 records were moved to the literature screening step. The combined totals for the 2013 and 2016 literature searches were 7,304 records identified; 4,928 records after removal of duplicates.

B.2.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies examining the health effects of glutaraldehyde:

- Title and Abstract Screen
- Full Text Screen

Title and Abstract Screen. Within the Endnote library, titles and abstracts were screened manually for relevance. Studies that were considered relevant were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study did not meet the inclusion criteria (Table B-1). In the Title and Abstract Screen step, 3,347 records were reviewed in 2013 and an additional 1,581 records were screened in 2016; 291 studies in 2013 and 13 studies in 2016 were considered relevant to Chapter 3 of the toxicological profile and were moved to the next step in the process.

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the Title and Abstract Screen step. Each study was reviewed to determine whether it met the inclusion criteria; however, the quality of the studies was not evaluated at this step of the process. Of the 291 studies in 2013 and 13 studies in 2016 undergoing Full Text Screen, 118 studies in 2013 and 13 records in 2016 did not meet the inclusion criteria; some of the excluded studies were used

as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

Summaries of the results of the literature search and screening for the draft for public comment profile (literature search conducted in 2013) and post-public comment profile (literature search conducted in 2016) are presented in Figures B-1 and B-2.

Figure B-1. Literature Search and Screen for Glutaraldehyde Health Effect Studies (January 2013)

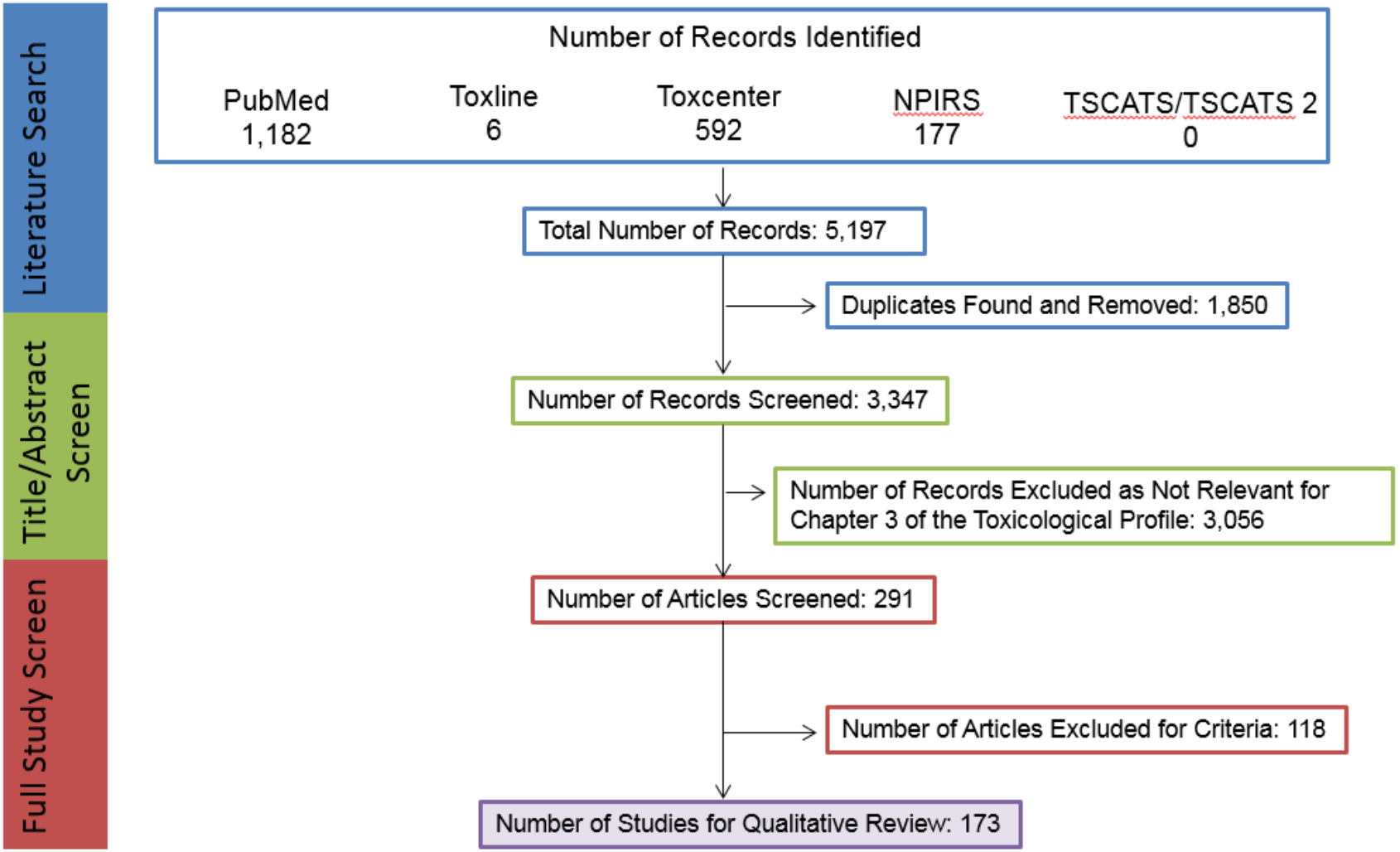
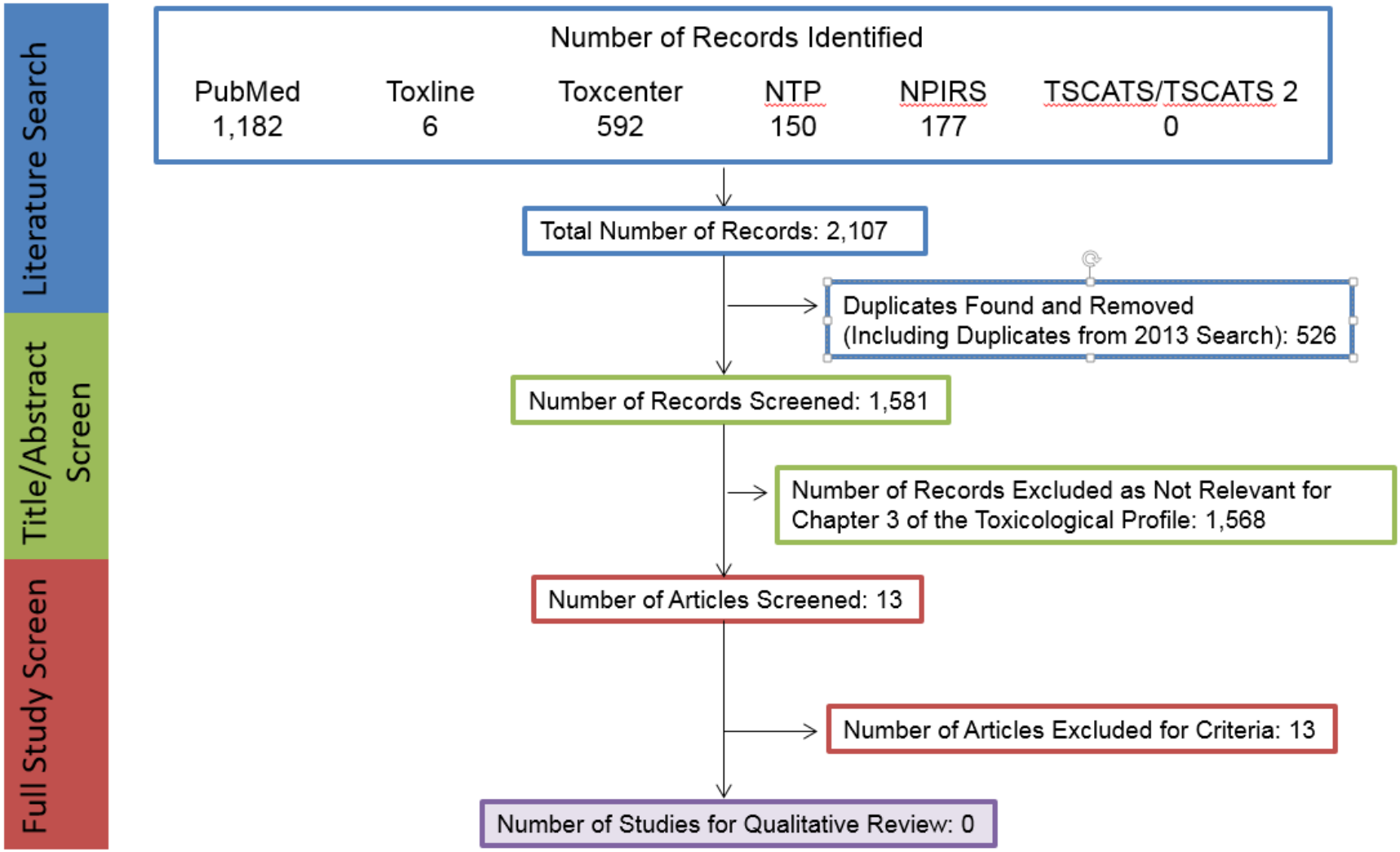


Figure B-2. Update Literature Search and Screen for Glutaraldehyde Health Effect Studies (November 2016)



B.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms in Distiller. A summary of the type of data extracted from each study is presented in Table B-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Document for Glutaraldehyde and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Section 3.2 of the profile and in the Levels Significant Exposures tables in Section 3.2 of the profile (Tables 3-1, 3-7, and 3-8, respectively).

B.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for glutaraldehyde identified in human and animal studies are presented in Tables B-3 and B-4, respectively. The available human studies examined a limited number of end points and reported respiratory, dermal, and ocular effects. Animal studies examined a number of end points following inhalation, oral, and dermal/ocular exposure. These studies reported respiratory, gastrointestinal, hematological, renal, dermal, ocular, body weight, and developmental effects. The hematological effects that were observed in one intermediate-duration inhalation exposure animal study were considered to be secondary to the nasal effects or were of questionable toxicological relevance due to the small magnitude of change. The body weight effects were not considered a primary effect and were likely secondary to the morbidity associated with the respiratory, gastrointestinal, or dermal effects. Similarly, the developmental effects appear to be secondary to maternal lethality (inhalation study) or taste aversion to glutaraldehyde-containing water. Thus, the available human and animal studies identify five potential health outcomes for glutaraldehyde: respiratory, gastrointestinal, renal, dermal, and ocular effects; the evidence streams for these outcomes were continued through Steps 5–8 of the systematic review. Animal studies have examined other potential end points, but did not find effects. For example, 16 animal studies examined the liver, but none of the studies reported an adverse effect. In the absence of human studies examining these potential outcomes, these data were considered inadequate for assessing the human hazard potential and were not continued through the systematic review process.

Table B-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

APPENDIX B

Table B-3. Overview of the Health Outcomes for Glutaraldehyde Evaluated In Human Studies

	Systemic effects												Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Other					
Inhalation studies																	
Cohort	6 6																
Case control																	
Population																	
Controlled exposure	3 3																
Oral studies																	
Cohort																	
Case control																	
Population																	
Controlled exposure																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Controlled Exposure									2 2	1 1							

Number of studies examining end point	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

Table B-4. Overview of the Health Outcomes for Glutaraldehyde Evaluated in Experimental Animal Studies

	Systemic effects												Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Other					
Inhalation studies																	
Acute-duration	11 11										3 2		2 0	2 0			
Intermediate-duration	8 7	2 0		2 1		3 0	2 0				2 2			2 0	2 0		
Chronic-duration	2 2	2 0	2 0	2 0		2 0	2 0	2 0			2 1			2 0	2 0		
Oral studies																	
Acute-duration			7 7	1 0		7 0	6 2				9 1					7 0	
Intermediate-duration	3 0		1 1	4 0		3 0	4 3			3 0	5 1				1 0	1 0	
Chronic-duration	1 1		2 2	1 0		1 0	1 0				1 1						
Dermal studies																	
Acute-duration									7 7	5 5	1 1						
Intermediate-duration																	
Chronic-duration																	

Number of studies examining end point	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

B.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

B.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's risk of bias questions (Rooney et al. 2014) and guidance for assessing risk of bias (NTP 2013b). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables B-5, B-6, and B-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table B-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance bias
Did researchers adhere to the study protocol?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Were the outcome assessors blinded to study group or exposure level?
Were the confounding variables assessed consistently across groups using valid and reliable measures?
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table B-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance bias
Did researchers adhere to the study protocol?
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Were the outcome assessors blinded to study group or exposure level?
Were the confounding variables assessed consistently across groups using valid and reliable measures?
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table B-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance bias
Were experimental conditions identical across study groups?
Did researchers adhere to the study protocol?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Were the outcome assessors blinded to study group or exposure level?
Were the confounding variables assessed consistently across groups using valid and reliable measures?
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of glutaraldehyde health effects studies (observational epidemiology, human experimental, and animal experimental studies) are presented in Tables B-8, B-9, and B-10, respectively.

Table B-8. Summary of Risk of Bias Assessment for Glutaraldehyde—Observational Epidemiology Studies

	Risk of bias criteria and ratings										
	Selection bias	Confounding bias		Performance bias	Attrition / exclusion bias	Detection bias				Selective reporting bias	
Reference	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Did researchers adhere to the study protocol?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects											
Cross-sectional cohort studies											
NIOSH 1987a	na	–	–	+	+	+	na	+	+	+	Second
NIOSH 1987b	na	–	–	+	+	+	na	+	+	+	Second
Pisaniello et al. 1997	+	–	–	+	+	+	na	+	+	+	Second
Cohort studies											
Norbäck 1988	+	+	–	+	+	+	na	+	+	+	First
Vyas et al. 2000	+	–	–	+	+	+	na	+	+	+	Second
Waters et al. 2003	+	–	–	+	+	+	na	+	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

APPENDIX B

Table B-9. Summary of Risk of Bias Assessment for Glutaraldehyde—Human-Controlled Exposure Studies

	Risk of bias criteria and ratings												
	Selection bias		Confounding bias		Performance bias		Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects													
Inhalation acute exposure													
Union Carbide Corp. 1976	+	na	+	+	+	+	++	na	na	+	+	+	First
Cain et al. 2007	+	na	+	+	+	+	++	na	na	+	+	+	First
Outcome: Dermal effects													
Dermal acute exposure													
Union Carbide Corp. 1966	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1980	+	+	+	+	+	+	+	+	+	+	+	+	First
Outcome: Ocular effects													
Ocular acute exposure													
Cain et al. 2007	+	na	+	+	+	+	++	na	na	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

APPENDIX B

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects														
Inhalation acute exposure														
Werley et al. 1995 (mouse)	+	+	+	+	++	+	+	+	+	+	++	++	+	First
Werley et al. 1995 (guinea pig)	+	+	+	+	+	+	+	+	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Zissu et al. 1994 (mouse)	+	+	+	+	+	+	+	+	+	na	++	++	+	First
Zissu et al. 1994 (mouse)	+	+	+	+	+	+	+	+	+	na	++	++	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Union Carbide Corp. 1992l (rat)	++	+	+	+	+	+	+	+	+	+	++	+	++	First
Union Carbide Corp. 1992d (rat)	++	+	+	+	+	+	+	++	+	+	++	++	++	First
Union Carbide Corp. 1992e (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure														
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Gross et al. 1994 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													Risk of bias tier
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Union Carbide Corp. 1992f (rat)	++	+	+	+	+	+	+	++	+	+	++	++	++	First
Inhalation chronic exposure														
NTP 1999; van Birgelen et al. 2000 (rat)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999 (rat)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999; van Birgelen et al. 2000 (mouse)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
NTP 1999 (mouse)	++	+	+	+	+	++	+	++	+	+	++	++	++	First
Outcome: Gastrointestinal effects														
Oral acute exposure														
BASF Corp. 1990l (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
BASF Corp. 1990m (rabbit)	+	+	+	+	+	+	+	++	+	+	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													Risk of bias tier
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	
BASF Corp. 1991a (rabbit)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
BASF Corp. 1991c (rat)	+	+	+	+	++	++	+	+	+	+	++	++	++	First
Union Carbide Chem & Plas Co. 1992 (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992a (rat)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992i (mouse)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Chem & Plas Co. 1991dd (dog)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Oral intermediate exposure														
Union Carbide Chem & Plas Co. 1991ee (dog)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													Risk of bias tier
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	
Oral chronic exposure														
van Miller et al. 2002 (rat)	+	+	+	+	+	++	+	++	+	na	+	+	+	First
Outcome: Renal effects														
Inhalation intermediate exposure														
NTP 1993 (rat)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
NTP 1993 (mouse)	+	+	+	+	++	++	+	++	+	+	++	++	++	First
Oral acute exposure														
BASF Corp. 1990l (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
BASF Corp. 1990m (rabbit)	+	+	+	+	+	+	+	++	+	+	+	+	+	First
BASF Corp. 1991c (rat)	+	+	+	+	++	++	+	+	+	+	++	++	++	First
BASF Corp. 1991c (rabbit)	+	+	+	+	++	++	+	+	+	+	++	++	++	First
Union Carbide Chem & Plas Co.	+	+	+	+	+	+	+	++	+	+	++	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
1991f (rat)														
Union Carbide Chem & Plas Co. 1991o (rat)	++	+	+	+	+	+	+	++	+	+	++	+	+	First
Oral intermediate exposure														
Union Carbide Chem & Plas Co. 1991w (mouse)	++	+	+	+	++	++	+	++	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991r (rat)	++	+	+	+	++	+	+	++	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991ee (dog)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Oral chronic exposure														
van Miller et al. 2002 (rat)	+	+	+	+	+	++	+	++	+	na	+	+	+	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Outcome: Dermal effects														
Dermal acute exposure														
Union Carbide Chem & Plas Co. 1991y (mouse)	++	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Chem & Plas Co. 1991aa (rabbit)	na	na	+	+	++	++	na	++	na	na	+	+	+	First
Union Carbide Corp. 1992a (rabbit)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992b (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992c (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Union Carbide Corp. 1992h (rabbit)	na	na	+	+	na	+	na	+	na	na	+	+	+	First
Dermal intermediate exposure														
Werley et al. 1996	+	+	+	+	+	++	+	++	+	+	++	++	++	First

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

Reference	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
(rat)														
Outcome: Ocular effects														
Inhalation acute exposure														
Hoechst Celanese Corp. 1981 (rat)	++	+	+	+	na	+	na	++	na	na	++	++	+	First
Union Carbide Corp. 1992e (rat)	+	+	+	+	+	+	+	+	+	+	+	+	+	First
Ocular Acute Exposure														
Union Carbide Chem & Plas Co. 1991cc (rabbit)	na	na	na	na	na	+	na	++	na	na	++	++	++	First
Union Carbide Chem & Plas Co. 1991k (rabbit)	na	na	+	+	na	+	na	+	na	na	+	+	+	First
Union Carbide Corp. 1992a (rabbit)	+	+	+	+	+	+	+	+	+	+	++	+	+	First
Union Carbide Corp. 1992b (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

APPENDIX B

Table B-10. Summary of Risk of Bias Assessment for Glutaraldehyde—Experimental Animal Studies

	Risk of bias criteria and ratings													
	Selection bias		Confounding bias		Performance bias			Attrition/ exclusion bias	Detection bias				Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Were experimental conditions identical across study groups?	Did researchers adhere to the study protocol?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Were the outcome assessors blinded to study group or exposure level?	Were the confounding variables assessed consistently across groups using valid and reliable measures?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?	Were all measured outcomes reported?	Risk of bias tier
Union Carbide Corp. 1992c (rabbit)	+	+	+	+	+	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

B.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to glutaraldehyde and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

B.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to glutaraldehyde and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in Tables B-11, B-12, and B-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table B-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table B-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table B-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, gastrointestinal, renal, dermal, and ocular effects observed in the observational epidemiology, human experimental, and animal experimental studies are presented in Tables B-14, B-15, and B-16, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table B-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table B-17.

Table B-14. Presence of Key Features of Study Design for Glutaraldehyde—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory effects					
Cross-sectional cohort studies					
NIOSH 1987a	No	Yes	Yes	No	Low
NIOSH 1987b	No	Yes	Yes	No	Low
Pisaniello et al. 1997	No	Yes	Yes	Yes	Moderate
Cohort studies					
Norbäck 1988	No	Yes	Yes	Yes	Moderate
Vyas et al. 2000	No	Yes	Yes	No	Low
Waters et al. 2003	No	Yes	Yes	Yes	Moderate

Table B-15. Presence of Key Features of Study Design for Glutaraldehyde—Human-Controlled Exposure Studies

Reference	Key feature				Initial study confidence
	Concurrent control group or self-control	Sufficient number of subjects tested	Appropriate methods to measure outcome	Adequate data for statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Union Carbide Corp. 1976	Yes	Yes	Yes	No	Moderate
Cain et al. 2007	Yes	Yes	Yes	No	Moderate
Outcome: Dermal effects					
Dermal acute exposure					
Union Carbide Corp. 1966	No	Yes	Yes	No	Low
Union Carbide Corp. 1980	No	Yes	Yes	No	Low
Outcome: Ocular Effects					
Ocular acute exposure					
Cain et al. 2007	Yes	Yes	Yes	No	Moderate

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Werley et al. 1995 (mouse)	Yes	No	Yes	Yes	Moderate
Werley et al. 1995 (guinea pig)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Zissu et al. 1994 (mouse)	Yes	Yes	Yes	Yes	High
Zissu et al. 1994 (mouse)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992l (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992d (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992e (rat)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (rat)	Yes	No	Yes	Yes	Moderate
Gross et al. 1994 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
Union Carbide Corp. 1992f (rat)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
NTP 1999; van Birgelen et al. 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 1999 (rat)	Yes	Yes	Yes	Yes	High
NTP 1999; van Birgelen et al. 2000 (mouse)	Yes	Yes	Yes	Yes	High
NTP 1999 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Gastrointestinal effects					
Oral acute exposure					
BASF Corp. 1990l (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1990m (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991a (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rat)	Yes	Yes	Yes	Yes	High

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Union Carbide Chem & Plas Co. 1992 (rat)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rat)	No	No	Yes	No	Very low
Union Carbide Corp. 1992i (mouse)	No	No	Yes	Yes	Low
Union Carbide Chem & Plas Co. 1991dd (dog)	Yes	No	Yes	No	Low
Oral intermediate exposure					
Union Carbide Chem & Plas Co. 1991ee (dog)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
van Miller et al. 2002 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects					
Inhalation intermediate exposure					
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
BASF Corp. 1990l (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1990m (rabbit)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rat)	Yes	Yes	Yes	Yes	High
BASF Corp. 1991c (rabbit)	Yes	Yes	Yes	Yes	High
Union Carbide Chem & Plas Co. 1991f (rat)	Yes	No	Yes	No	Low
Union Carbide Chem & Plas Co. 1991o (rat)	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Union Carbide Chem & Plas Co. 1991w (mouse)	Yes	Yes	Yes	No	Moderate
Union Carbide Chem & Plas Co. 1991r (rat)	Yes	Yes	Yes	No	Moderate
Union Carbide Chem & Plas Co. 1991ee (dog)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
van Miller et al. 2002 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Dermal effects					
Dermal acute exposure					
Union Carbide Chem & Plas Co. 1991y (mouse)	Yes	No	Yes	Yes	Moderate
Union Carbide Chem & Plas Co. 1991aa (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992b (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992c (rabbit)	No	No	Yes	No	Very low

Table B-16. Presence of Key Features of Study Design for Glutaraldehyde—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Union Carbide Corp. 1992h (rabbit)	No	No	Yes	No	Very low
Dermal intermediate exposure					
Werley et al. 1996 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Ocular effects					
Inhalation acute exposure					
Hoechst Celanese Corp. 1981 (rat)	No	Yes	Yes	Yes	Moderate
Union Carbide Corp. 1992e (rat)	Yes	Yes	Yes	Yes	High
Ocular acute exposure					
Union Carbide Chem & Plas Co. 1991cc (rabbit)	No	Yes	Yes	Yes	Moderate
Union Carbide Chem & Plas Co. 1991k (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992a (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992b (rabbit)	No	No	Yes	No	Very low
Union Carbide Corp. 1992c (rabbit)	No	No	Yes	No	Very low

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Human studies		
Cross-sectional cohort studies		
NIOSH 1987a	Low	
NIOSH 1987b	Low	Moderate
Pisaniello et al. 1997	Moderate	
Cohort studies		
Norbäck 1988	Moderate	
Vyas et al. 2000	Low	Moderate
Waters et al. 2003	Moderate	
Controlled exposure		
Union Carbide Corp. 1976	Moderate	Moderate
Cain et al. 2007	Moderate	
Animal studies		
Werley et al. 1995 (mouse)	Moderate	
Werley et al. 1995 (guinea pig)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	High
Zissu et al. 1994 (mouse)	High	
Zissu et al. 1994 (mouse)	High	
Union Carbide Corp. 1992l (rat)	High	
Union Carbide Corp. 1992d (rat)	High	
Union Carbide Corp. 1992e (rat)	High	
Inhalation intermediate exposure		
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
Gross et al. 1994 (rat)	Moderate	
Gross et al. 1994 (mouse)	Moderate	
NTP 1993 (mouse)	Moderate	High
NTP 1993 (rat)	Moderate	
NTP 1993 (mouse)	High	
NTP 1993 (rat)	High	
Union Carbide Corp. 1992f (rat)	Moderate	
Inhalation chronic exposure		
Animal studies		
NTP 1999; van Birgelen et al. 2000 (rat)	High	High
NTP 1999 (rat)	High	

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1999; van Birgelen et al. 2000 (mouse)	High	
NTP 1999 (mouse)	High	
Outcome: Gastrointestinal effects		
Oral acute exposure		
Animal studies		
BASF Corp. 1990l (rat)	High	
BASF Corp. 1990m (rabbit)	High	
BASF Corp. 1991a (rabbit)	High	
BASF Corp. 1991c (rat)	High	High
Union Carbide Chem & Plas Co. 1992 (rat)	Very low	
Union Carbide Corp. 1992a (rat)	Very low	
Union Carbide Corp. 1992i (mouse)	Low	
Union Carbide Chem & Plas Co. 1991dd (dog)	Low	
Oral intermediate exposure		
Animal studies		
Union Carbide Chem & Plas Co. 1991ee (dog)	Moderate	Moderate
Oral chronic exposure		
Animal studies		
van Miller et al. 2002 (rat)	High	High
Outcome: Renal effects		
Inhalation intermediate exposure		
Animal studies		
NTP 1993 (rat)	High	High
NTP 1993 (mouse)	High	
Oral acute exposure		
Animal studies		
BASF Corp. 1990l (rat)	High	
BASF Corp. 1990m (rabbit)	High	
BASF Corp. 1991c (rat)	High	High
BASF Corp. 1991c (rabbit)	High	
Union Carbide Chem & Plas Co. 1991f (rat)	Low	
Union Carbide Chem & Plas Co. 1991o (rat)	Moderate	
Oral intermediate exposure		
Animal studies		
Union Carbide Chem & Plas Co. 1991w (mouse)	Moderate	
Union Carbide Chem & Plas Co. 1991r (rat)	Moderate	Moderate
Union Carbide Chem & Plas Co. 1991ee (dog)	Moderate	
Oral chronic exposure		
Animal studies		
van Miller et al. 2002 (rat)	High	High

Table B-17. Initial Confidence Rating for Glutaraldehyde Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Dermal effects		
Dermal acute exposure		
Human studies		
Controlled exposure		
Union Carbide Corp. 1966 (irritation)	Low	Low
Union Carbide Corp. 1980 (irritation)	Low	
Animal studies		
Union Carbide Chem & Plas Co. 1991y (mouse)	Moderate	
Union Carbide Chem & Plas Co. 1991aa (rabbit)	Very low	
Union Carbide Corp. 1992a (rabbit)	Very low	Moderate
Union Carbide Corp. 1992b (rabbit)	Very low	
Union Carbide Corp. 1992c (rabbit)	Very low	
Union Carbide Corp. 1992h (rabbit)	Very low	
Dermal intermediate exposure		
Animal studies		
Werley et al. 1996 (rat)	High	High
Outcome: Ocular effects		
Ocular acute exposure (airborne vapor)		
Human studies		
Controlled exposure		
Cain et al. 2007	Moderate	Moderate
Animal studies		
Hoechst Celanese Corp. 1981 (rat)	Moderate	High
Union Carbide Corp. 1992e (rat)	High	
Ocular acute exposure (ocular instillation)		
Animal studies		
Union Carbide Chem & Plas Co. 1991cc (rabbit)	Moderate	
Union Carbide Corp. 1992h (rat)	Very low	
Union Carbide Corp. 1992a (rabbit)	Very low	Moderate
Union Carbide Corp. 1992b (rabbit)	Very low	
Union Carbide Corp. 1992c (rabbit)	Very low	

B.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, gastrointestinal, renal, dermal, and ocular effects are presented in Table B-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with glutaraldehyde exposure is presented in Table B-19.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables B-14, B-15, and B-16). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the end points to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Table B-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory Effects			
Cross-sectional cohort studies	Moderate	None	Moderate
Cohort studies	Moderate	-1 for risk of bias: studies in risk of bias second tier	Low
Human controlled exposure studies	Moderate	+1 for consistency: threshold levels were consistent across studies	High
Animal studies	High	None	High
Outcome: Gastrointestinal Effects			
Animal studies	High	None	High
Outcome: Renal Effects			
Animal studies	High	None	High
Outcome: Dermal Effects			
Human controlled exposure studies	Low	None	Low
Animal studies	High	None	High
Outcome: Ocular Effects			
Human controlled exposure studies	Moderate	None	Moderate
Animal studies	High	+1 consistency: effects were consistently observed	High

Table B-19. Confidence in the Body of Evidence for Glutaraldehyde

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	High	High
Gastrointestinal effects	No data	High
Renal effects	No data	High
Dermal effects	Low	High
Ocular effects	Moderate	High

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient

  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

B.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for glutaraldehyde, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence which was established in the sixth step of the systematic review (Section B.6) and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome

A summary of the level of evidence of health effects for glutaraldehyde is presented in Table B-20.

Table B-20. Level of Evidence of Health Effects for Glutaraldehyde

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	High	Health effect (inhalation only)	High
Gastrointestinal effects	No data	No data	No data
Renal effects	No data	No data	No data
Dermal effects	Low	Health effect (dermal contact)	Low
Ocular effects	Moderate	Health effect (ocular contact)	Moderate
Animal studies			
Respiratory effects	High	Health effect (inhalation only)	High
Gastrointestinal effects	High	Health effect (oral only)	High
Renal effects	High	Health effect (inhalation, oral)	High
Dermal effects	High	Health effect (dermal contact)	High
Ocular effects	High	Health effect (ocular contact)	High

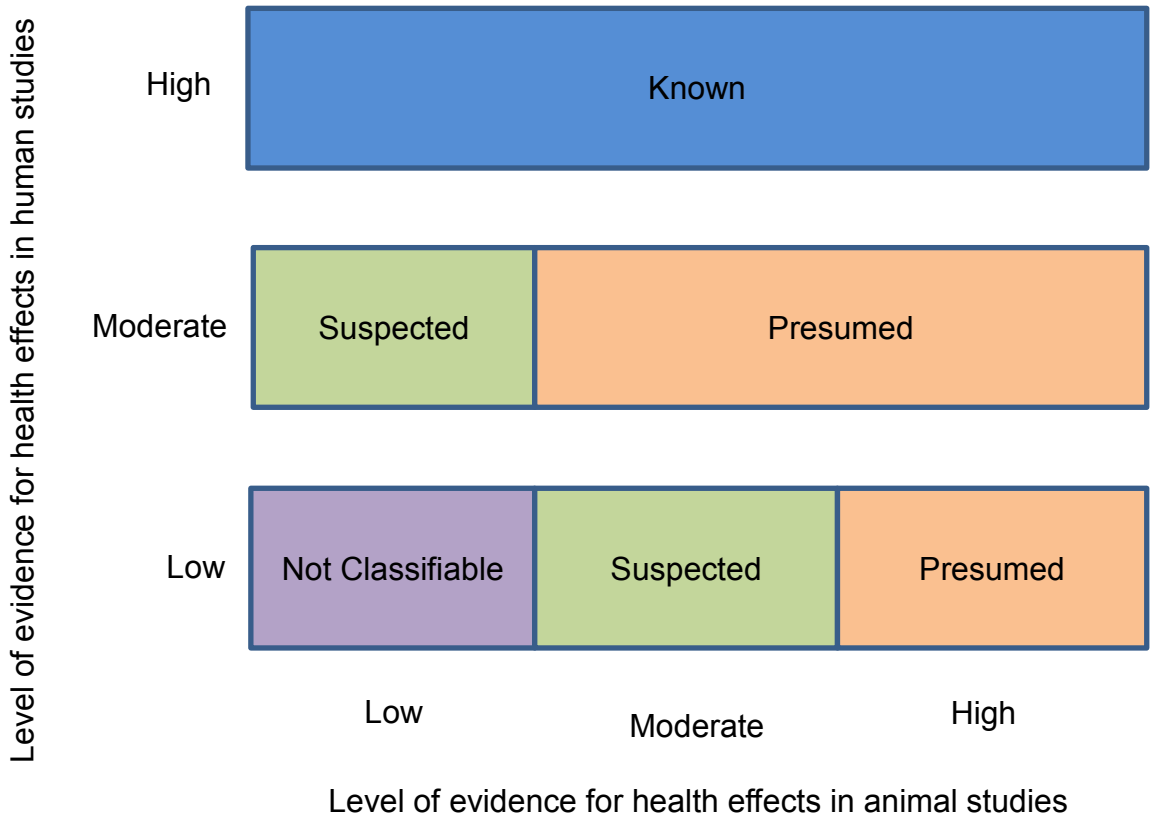
B.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure B-3 and described below.

Figure B-3. Hazard Identification Scheme



- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for glutaraldehyde are presented in Table B-21.

Table B-21. Hazard Identification Conclusions for Glutaraldehyde

Outcome	Hazard identification
Respiratory effects	Known health effect following inhalation exposure
Gastrointestinal effects	Presumed health effect following oral exposure
Renal effects	Presumed health effect
Dermal effects	Presumed health effect following dermal exposure
Ocular effects	Presumed health effect following ocular exposure

APPENDIX C. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page C-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page C-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

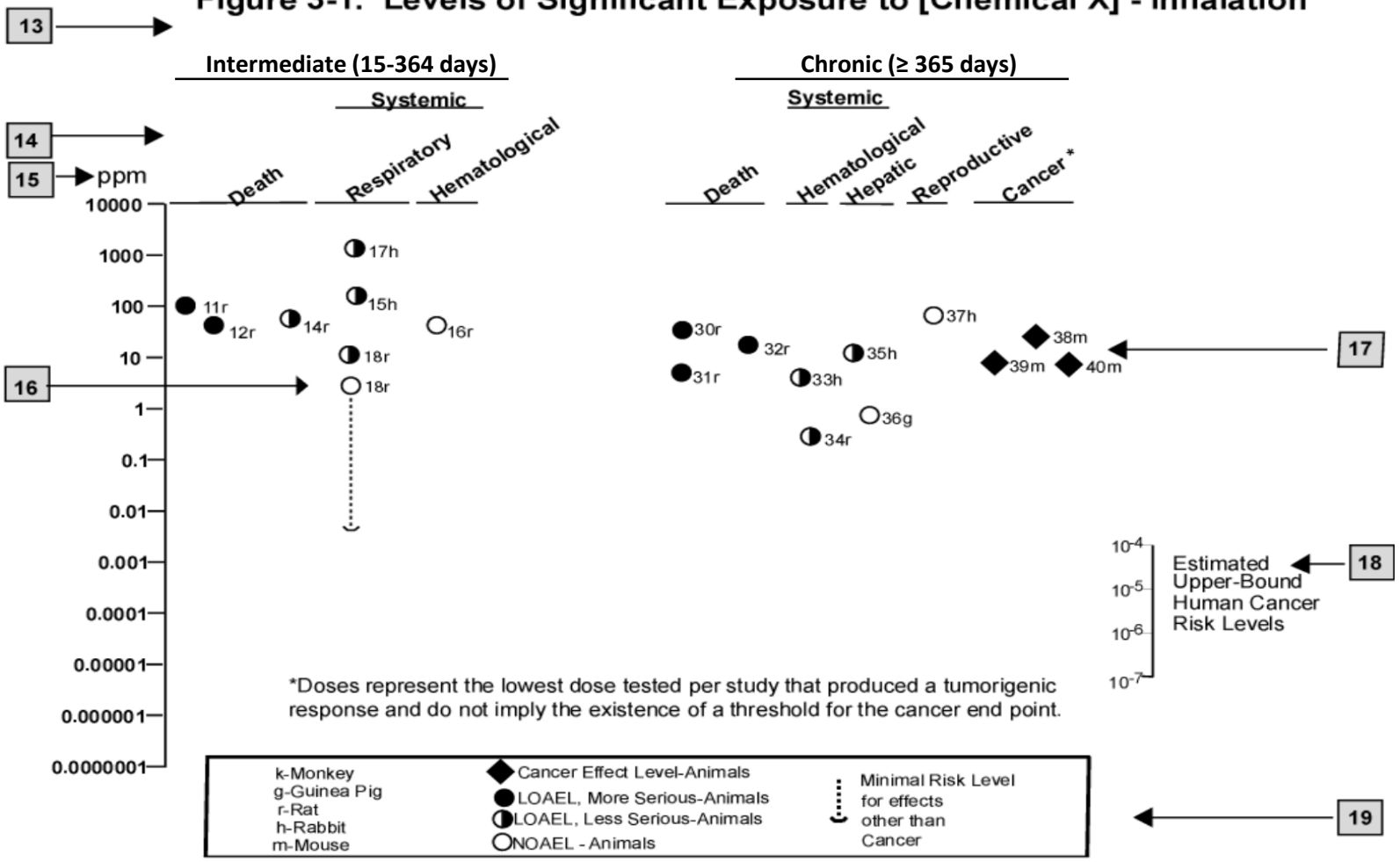
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



This page is intentionally blank.

APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result