

**Disposition of Peer Review Comments for
Toxicological Profile for Glutaraldehyde**

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Prepared for:

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Responses to comments on pre-public draft 5 of the Toxicological Profile for Glutaraldehyde that was provided to the reviewers by ATSDR.

Comments that were purely stylistic in nature were addressed at the discretion of ATSDR and do not appear in this formal disposition. Several comments were of a nature that did not require a formal response. Comments that warranted a formal response are listed below.

Comments provided by Reviewer #1:

General Comments

COMMENT: Reviewer #1 stated: “The NTP cancer studies are alternately described as 2-year or 104 weeks. Both are correct, but for clarity to the lay reader, one or the other time measurement should be used consistently.”

RESPONSE: *All references to the study duration as 104 weeks were changed to 2 years.*

COMMENT: Reviewer #1 stated: “The glutaraldehyde test data in the NTP toxicity (1993) and carcinogenicity (1999) reports also appear in peer-reviewed journal articles, e.g., Haworth et al., 1983, Dillon et al., 1998, and van Birgelen et al. 2000, all of which are cited in the draft. Referencing both the NTP and journal articles to support the same statement in the body of the report suggests that there was more than one study and they all agreed on the results. It should be made clear that the NTP and Haworth or van Birgelen references contain the same test data, but in different reports. Additionally, the NTP 1993 and 1999 reports contain the same genotoxicity data as are in the Haworth et al 1993 and Galloway et al. 1985 publications.”

RESPONSE: *Although true, an explanation would be lengthy. String references to the same data should provide sufficient indication that information is from a common source, particularly for the genotoxicity tabular results where each row is dedicated to a single set of assays. No change was made.*

COMMENT: Reviewer #1 stated: “With regard to the interpretation of the apparently contradictory Salmonella mutagenicity results, which is very evident in Table 3-8, some of the differences in response may be a function of the specific test protocol used, e.g., plate test, preincubation test, fluctuation test.”

RESPONSE: *The following statement was added to the summary in Section 3.3: “Variability in test protocol among the various mutagenicity assays may be responsible for at least some of the variability in results.”*

COMMENT: Section 7.3.2 Ongoing Studies: Reviewer #1 questioned: “Should there be as ‘as of’ date attached to this sentence, because the date on the final document will not be the date of the most recent literature search.”

RESPONSE: *A citation date (RePORTER 2014) was added to Section 3.13.3 and the search date was included in the reference added to Chapter 9.*

Comments on Charge Questions and Statements from the Guidelines for Peer Review of ATSDR's Toxicological Profiles

CHAPTER 1. PUBLIC HEALTH STATEMENT

Charge question and statement: “Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.”

COMMENT: Reviewer #1 made several suggestions for wording changes in sections titled “Where is Glutaraldehyde Found?”. The Reviewer also suggested that a statement indicating that glutaraldehyde would quickly degrade in water should be added to the next-to-last paragraph of this section.

RESPONSE: *The suggested wording changes were made. A statement that glutaraldehyde would quickly degrade in water was already present in the referenced paragraph.*

CHAPTER 3. HEALTH EFFECTS

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Toxicity – Quality of Human Studies

Charge question and statement: “Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.”

COMMENT: Reviewer #1 stated: “A number of abbreviations and acronyms are defined in the body of the document but not in Appendix D, e.g., BMCLx, NOAELHEC, BMCLHEC, IPCS.”

RESPONSE: *The requested additions were made to Appendix D.*

Section 3.3 GENOTOXICITY

COMMENT: Reviewer #1 stated that glutaraldehyde was also nonmutagenic in Salmonella strains TA7001-6 and cited Kamber et al. 2009 as the source.

RESPONSE: *The results from Kamber et al. (2009) were added to Section 3.3.*

COMMENT: Reviewer #1 stated that the report of Galloway et al. (1985) contains studies from two laboratories performing the same protocols on the same glutaraldehyde samples for both chromosome aberrations and sister chromatid exchanges. The reviewer noted that results from two laboratories in another report (Haworth et al. 1983) are summarized separately in Table 3-8 and indicated that the studies of Galloway et al. (1985) should be summarized separately as well.

RESPONSE: *The requested change was made.*

COMMENT: **Table 3-9, entry for chromosomal aberrations in mouse bone marrow from NTP (1999).** Reviewer #1 stated “It is misleading (and incorrect) to report the bone marrow results as +/- [i.e., equivocal result]. The test protocol called for the two sampling times in order to detect effects that may

not appear at the earlier sampling time because of cell cycle delay or other toxicity. Therefore, the overall result should be listed as ‘+’. The footnote can be used to denote that the result was time-sensitive.”

RESPONSE: *The requested change was made. The footnote denotes that the result was time-sensitive.*

COMMENT: Reviewer #1 stated that the type of DNA damage cited to Speit et al. (2008) should be specified in the summary of results in Section 3.3.

RESPONSE: *The requested addition was made.*

COMMENT: Reviewer #1 stated that the word “assays” in the context of the sentence “In assays that employed Syrian hamster embryo cells, glutaraldehyde did not induce unscheduled DNA synthesis either in the presence or absence of exogenous metabolic activation (Zeiger et al. 2005), or cell transformation in the absence of exogenous metabolic activation (Yamaguchi and Tsutsui 2003)” implies that three test types were employed, and that if so, the specific test types should be identified.

RESPONSE: *The phrase “assays that employed” was removed from the sentence.*

COMMENT: Reviewer #1 stated that the summary statement in the final paragraph of Section 3.3 is “misleading and an incorrect assessment of how the Salmonella mutagenicity test is interpreted. Glutaraldehyde is weakly mutagenic in bacteria because it was positive in at least one of the Salmonella strains. Saying that it is ‘mutagenic in at least some bacterial strains’ is equivalent to saying that a substance is carcinogenic in at least some organs of the body”.

RESPONSE: *The text was revised to read “... glutaraldehyde is weakly mutagenic in bacteria and mammalian cell lines.”*

CHAPTER 9. REFERENCES

Charge question and statement: “Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.”

COMMENT: Reviewer #1 attached a file containing the study of Kamber et al. (2009).

RESPONSE: *The identified study (Kamber et al. 2009) was added to Chapter 9 and was cited in Section 3.3 and Table 3-8.*

Reviewer #1 peer-review of unpublished studies cited in the ATSDR Toxicological Profile for Glutaraldehyde (pre-public comment draft 5)

Reviewer #1 provided a spreadsheet that described available study design data, adequacy (design, methods, and reporting), results, and conclusions, as well as the Reviewer's opinion regarding validity of study author conclusions and inadequacies/confounders, and the Reviewer's conclusions and comments. The following table summarizes Reviewer #1 conclusions regarding adequacy of study report and the Reviewer's conclusions and comments for each of the unpublished studies.

Reference	Reviewer #1 evaluation of study quality			Reviewer's conclusions	Reviewer's comments
	Design	Methods	Reporting		
BASF 2013					Summary results from numerous tox studies
BASF Corp. 1990f	Adequate	Adequate	Minimal data included	Irritant	Identical test dose and conditions to BASF Corp. 1990g, but overlapping dates
BASF Corp. 1990g	Adequate	Adequate	Minimal data included	Irritant	Identical test dose and conditions to BASF Corp. 1990f, but overlapping dates
BASF Corp. 1990i	Adequate	Adequate	Inadequate	Toxic; M>F	More toxic in males than females; not commented upon. Exp. date overlaps 1990f and 1990f studies.
BASF Corp. 1990j	Adequate	Adequate	Minimal data included	Agree	
BASF Corp. 1990k	Insufficient info	Insufficient info	Inadequate	Cannot draw conclusion	
BASF Corp. 1990l	Not described	Not described	Detailed summary data tables only	Cannot draw conclusion	Appears to be a well-conducted study, but the report does not contain protocol information or draw any conclusions
BASF Corp. 1990m	Not described	Not described	Detailed summary data tables only	Cannot draw conclusion	Appears to be a well-conducted study, but the report does not contain protocol information or draw any conclusions
BASF Corp. 1991a	Adequate	Adequate	Adequate	Agree	Complete GLP report
BASF Corp. 1991b	Adequate	Adequate	Adequate	Agree	Complete GLP report
BASF Corp. 1991c	?	?	?	Cannot draw conclusion	Appears to be a well-conducted study, but the report does not contain protocol information or draw any conclusions
Confidential1974	?	?	?	Cannot draw conclusion	Barely readable copy; some sections unreadable
Confidential 1987a	Adequate	Adequate	Adequate	Agree	

Reference	Reviewer #1 evaluation of study quality			Reviewer's conclusions	Reviewer's comments
	Design	Methods	Reporting		
Confidential 1987b	Adequate	Confusing	Confusing	No apparent effect	Not clearly written. M&M and graphs have TEM as +ve control; tables have MMS
Confidential 1987c	Adequate	Adequate	Adequate	No effect	
Confidential 1991	?	?	Inadequate	Cannot draw conclusion	Too little information on methodology or protocol
Confidential 2002	Not described	Not described	Inadequate	Cannot draw conclusion re carcinogenicity	no information on methodology or protocol
Hoechst Celanese Corp. 1981	Adequate	Adequate	Adequate	Agree	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991s	Not described	Not described	Inadequate	Cannot draw conclusion	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991bb	Adequate	Adequate	Adequate	Minimal effects	
Union Carbide Chem & Plas Co. 1991cc	Adequate	Adequate	Adequate	Corneal injury	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1992	Adequate	Adequate	Adequate	Toxic	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991b	Inadequate	Inadequate	Inadequate	?	Summary results only; no methods info. No animal data or observation notes
Union Carbide Chem & Plas Co. 1991e	Insufficient info	Insufficient info	Inadequate	?	Ucaricide antimicrobial formulation tested. Summary data from multiple studies in different species and by different routes
Union Carbide Chem & Plas Co. 1991f	Adequate	Adequate	Adequate	Decreased water, food intake	
Union Carbide Chem & Plas Co. 1991k	Adequate	Adequate	Inadequate	Dermal toxic	
Union Carbide Chem & Plas Co. 1991l	Insufficient info	Insufficient info	Inadequate	Toxic at high doses	Confusing; results from two studies appear to be intermingled
Union Carbide Chem & Plas Co. 1991m	Insufficient info	Insufficient info	Inadequate	Insufficient data presented	Multiple trials with different doses

Reference	Reviewer #1 evaluation of study quality			Reviewer's conclusions	Reviewer's comments
	Design	Methods	Reporting		
Union Carbide Chem & Plas Co. 1991o	Adequate	Adequate	Inadequate	Insufficient data presented	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991p	Adequate	Adequate	Inadequate	Insufficient data presented	Aquacar formulation tested
Union Carbide Chem & Plas Co. 1991q	Adequate	Adequate	Adequate	Agree	
Union Carbide Chem & Plas Co. 1991r	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Chem & Plas Co. 1991t	Inadequate	Insufficient info	Adequate	Agree	
Union Carbide Chem & Plas Co. 1991v	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Chem & Plas Co. 1991w	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Chem & Plas Co. 1991x	Adequate	Adequate	Inadequate	Insufficient data presented	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991y	Adequate	Adequate	Adequate	Agree	
Union Carbide Chem & Plas Co. 1991z	Adequate	Adequate	Adequate	Agree	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991aa	Adequate	Adequate	Adequate	Dermal toxic	Ucaricide antimicrobial formulation tested
Union Carbide Chem & Plas Co. 1991dd	Adequate	Adequate	Inadequate	Agree	Insufficient information on protocols; not test data presented.
Union Carbide Chem & Plas Co. 1991ee	Adequate	Adequate	Inadequate	Insufficient data presented	Summary text only. No test data are presented.
Union Carbide Chem & Plas Co. 1991ff	Adequate	Adequate	Adequate	Adequate study	
Union Carbide Chem & Plas Co. 1991gg	Adequate	Adequate	Adequate	Negative for all endpoints	
Union Carbide Chem & Plas Co. 1991hh	Questionable	Adequate	Adequate	Negative without s9; questionable test with s9	The absence of any mutants at any glutaraldehyde concentration, is curious and the test should have been repeated

Reference	Reviewer #1 evaluation of study quality			Reviewer's conclusions	Reviewer's comments
	Design	Methods	Reporting		
Union Carbide Chem & Plas Co. 1991ii	Adequate	Adequate	Adequate	Agree	
Union Carbide Chem & Plas Co. 1991jj	Questionable	Adequate	Adequate	Agree	Ucaricide antimicrobial formulation tested
Union Carbide Corp. 1966	Adequate	Adequate	Adequate	Adequate study	
Union Carbide Corp. 1976	Adequate	Adequate	Inadequate	Insufficient data presented	Cidex solution tested
Union Carbide Corp. 1980	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Corp. 1992a	Insufficient info	Insufficient info	Inadequate	Cannot draw conclusion	Range-finding study; minimal information
Union Carbide Corp. 1992b	Insufficient info	Insufficient info	Partial adequate	Cannot draw conclusion	Range-finding study; minimal information
Union Carbide Corp. 1992c	Insufficient info	Insufficient info	Partial adequate	Cannot draw conclusion	
Union Carbide Corp. 1992d	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Corp. 1992e	Adequate	Adequate	Adequate	Agree	
Union Carbide Corp. 1992f	Adequate	Adequate	Inadequate	Insufficient data presented	
Union Carbide Corp. 1992g	Inadequate	Adequate	Inadequate	Insufficient data presented	Experiment designed primarily to monitor generation of vapor, and chamber concentrations
Union Carbide Corp. 1992h	Adequate	Adequate	Adequate	Agree	Both ucaricide and glutaraldehyde tested
Union Carbide Corp. 1992i	Adequate	Adequate	Adequate	Agree	
Union Carbide Corp. 1992j	Adequate	Adequate	Adequate	Agree	Ucaricide antimicrobial formulation tested
Union Carbide Corp. 1992k	Adequate	Adequate	Adequate	Agree	Ucaricide antimicrobial formulation tested
Union Carbide Corp. 1992l	Adequate	Adequate	Adequate	Toxic at all doses	
Union Carbide Corp. 1993a	Adequate	Adequate	Summary data only	Insufficient data presented	Ucaricide antimicrobial formulation tested. No summary data tables; only crude result ranges noted in report

Reference	Reviewer #1 evaluation of study quality			Reviewer's conclusions	Reviewer's comments
	Design	Methods	Reporting		
Union Carbide Corp. 1993b	Adequate	Adequate	Inadequate	Insufficient data presented	Ucaricide antimicrobial formulation tested
Union Carbide Corp. 1996	Adequate	Adequate	Inadequate	Cannot draw conclusion	Cidex preparation used
Ballantyne 1995					Summary review document of human and animal studies based on unpublished industry studies and peer-reviewed articles.

RESPONSE: ATSDR reviewed the evaluations of the unpublished studies provided by Reviewer #1 and determined that the following studies did not provide adequate data for inclusion in the ATSDR Toxicological Profile for Glutaraldehyde; these studies were removed from the profile: BASF Corp. 1990k; Confidential 1991; Union Carbide Chem & Plas Co. 1991b, 1991e, 1991s; Union Carbide Corp. 1992g, 1992k, 1996.

Comments provided by Reviewer #2:

Reviewer #2 submitted an electronic file in which comments were categorized according to location within the draft of the Toxicological Profile for Glutaraldehyde provided to the reviewer. In this formal disposition of peer review comments, each comment is identified by Chapter (C), page (P), and line (L) to which the comment relates. Some comments refer to selected tables or figures in the toxicological profile and are identified as such.

COMMENT: C3, Table 3-1: Reviewer #2 suggested that ATSDR check entries numbered 10 (Union Carbide Corp. 1976), 13 (Union Carbide Corp. 1992k), and 16 (Union Carbide Corp. 1992d) in Table 3-1 (Levels of Significant Exposure to Glutaraldehyde – Inhalation) and consider amending these entries based on the Reviewer’s comments on these unpublished studies.

RESPONSE: *Responses to the comments on these studies are found in the section below that deals with formal disposition of comments on unpublished studies.*

COMMENT: C3, Table 3-5: Reviewer #2 suggested that ATSDR check entries numbered 2 (Union Carbide Corp. 1992b), 4 (Union Carbide Corp. 1992a), 5 (Union Carbide Chem & Plas Co. 1991z), 6 (Union Carbide Chem & Plas Co. 1991t), 8 (Union Carbide Corp. 1992c), 27 (Union Carbide Chem & Plas Co. 1991o), 30 and 38 (BASF Corp. 1990m), and 48 (BASF Corp. 2013; Confidential 2002) in Table 3-5 (Levels of Significant Exposure to Glutaraldehyde – Oral) and consider amending these entries based on the Reviewer’s comments on these unpublished studies.

RESPONSE: *Responses to the comments on these studies are found in the section below that deals with formal disposition of comments on unpublished studies.*

COMMENT: C3, Table 3-6: Reviewer #2 suggested that ATSDR check the following references in Table 3-6 (Levels of Significant Exposure to Glutaraldehyde – Dermal) and consider amending Table 3-5 based on the Reviewer’s comments on these unpublished studies: BASF Corp. 1990l; Union Carbide Chem & Plas Co. 1991aa; Union Carbide Corp. 1992a, 1992b, 1992c.

RESPONSE: *Responses to the comments on these studies are found in the section below that deals with formal disposition of comments on unpublished studies.*

COMMENT: C3.2.1.1, P14, L18+: Reviewer #2 stated that the description of “static” and “dynamic” conditions are not understandable and that the exposure concentrations are not well described in the referenced reports.

RESPONSE: *A statement was added to note that static conditions means evaporation of test substance in test chamber and dynamic conditions include procedures that can generate higher vapor concentrations than those achieved under static conditions.*

COMMENT: C3.2.1.2, P15, L21+ (Table 3-2): Reviewer #2 stated that Table 3-2 is well described, but noted that the “respiratory effects” are not systemic effects, but rather local effects.

RESPONSE: *Although ATSDR agrees that the effects of glutaraldehyde vapor on the upper respiratory tract are contact irritative effects in nature, the format of ATSDR toxicological profiles is such that these local effects are described within the category of respiratory effects.*

COMMENT: C3.4, Figure 3-4: Reviewer #2 stated that the print in the lower portion of Figure 3-4 was difficult to read on the printed copy.

RESPONSE: *Figure 3-4 was reviewed and the font style and size is consistent throughout the figure, with the exception of the chemical structures for glutacetyl coenzyme A and crotonyl coenzyme A, which are slightly smaller due to space constraints.*

COMMENT: C3.12, P90, first paragraph: Reviewer #2 does not agree with the statement that additional animal studies are needed to quantitatively assess the sublethal acute oral toxicity of glutaraldehyde. The Reviewer considers such studies to be a waste of animals. The Reviewer indicated the need for a well-controlled volunteer study on human chemosensory and behavioral effects of glutaraldehyde according to modern experimental standards.

RESPONSE: *The text was revised to indicate that additional animal studies do not appear necessary, but that an animal study could be designed to quantitatively assess the sublethal acute oral toxicity of glutaraldehyde.*

Reviewer #2 evaluation of unpublished studies cited in the ATSDR Toxicological Profile for Glutaraldehyde

Regarding review of unpublished studies provided for review, Reviewer #2 stated the following:

“I was asked to review unpublished information on glutaraldehyde, thereby observing the following points:

- adequacy of design, methodology, and reporting;
- validity of results and author's conclusions;
- study inadequacies or confounding factors.

As an approach to evaluate the quality of a documentation of toxicological data in a comparative way, I have used the evaluation criteria, which were published by HJ Klimmisch, A Andrae and U Tillmann (‘A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data’, Regul Toxicol Pharmacol 25:1-5, 1997).

In brief, this system leads to the assignment of an individual study report into one of the following evaluation categories (‘codes’):

- 1 Reliable without restriction: fulfillment of GLP (or similar) criteria, all parameters described closely/comparable to a guideline method.
- 2 Reliable with restriction: test parameters documented not totally complying with the specific testing guideline, but sufficient to accept the data which are nevertheless well documented and scientifically acceptable.
- 3 Not reliable: non-physiological pathways of application, method not acceptable, documentation not sufficient, not convincing for an expert judgment.
- 4 Not assignable: No sufficient experimental details, e.g., short abstract, or secondary literature.

In the following, I follow the general sequence of reports as listed in ‘Cited Studies in the ATSDR Toxicological Profile for Glutaraldehyde to be Peer-Reviewed’, with addition of studies that were received separately.”

COMMENT: Ballantyne 1995; Reviewer #2 stated: “This is a DOW-internal review article that provides a reliable overview of toxicological data that was available at that time (1995). It is not an original study report. Nevertheless, it provides a solid introduction into the topic and overview. As a study report, not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Ballantyne (1995) reference was retained.*

COMMENT: BASF Corp. 1990f; Reviewer #2 stated: “A primary skin irritation study in 6 rabbits with 50% glutaraldehyde, dated 1982. Conclusion of glutaraldehyde being a severe primary irritant. The pre-GLP study appears to be performed correctly, but documentation is limited. Reliable with restrictions, but in general scientifically acceptable (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The BASF Corp. (1990f) reference was retained.*

COMMENT: BASF Corp. 1990g; Reviewer #2 stated: “A primary skin irritation study in 6 rabbits with 25% glutaraldehyde, dated 1982. Conclusion of glutaraldehyde being a severe primary irritant. The pre-GLP study appears to be performed correctly, but documentation is limited. Reliable with restrictions, but in general scientifically acceptable (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The BASF Corp. (1990g) reference was retained.*

COMMENT: BASF Corp. 1990i; Reviewer #2 stated: “A dermal LD50 study with 50% glutaraldehyde with a limited number of rabbits. The calculated LD50 was said to be 16.5 ml/kg (located between group 2 of 10 ml/kg and group 3 of 20 ml/kg). Study dated 1982, with very limited documentation. Note: Although lethality in the highest dose group was 100%, the text says that observations were unremarkable, and all rabbits appeared active and healthy. Therefore not reliable (code 3).”

RESPONSE: *The observations are considered to apply to the survivors, not the decedents. The BASF Corp. (1990i) reference was retained.*

COMMENT: BASF Corp. 1990j; Reviewer #2 stated: “An oral LD50 study with 50% glutaraldehyde in 25 male and 25 female Wistar rats, dated 1982. Although documentation is limited, the study and its statistical evaluation appear to be performed correctly. Pre-GLP study, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The BASF Corp. (1990j) reference was retained.*

COMMENT: BASF Corp. 1990k; Reviewer #2 stated: “Buehler test in Guinea pigs for sensitization with 50% glutaraldehyde, dated 1982. No solid description of the experiments; the text itself is difficult to understand. Therefore not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The BASF Corp. (1990k) reference was deleted from the toxicological profile.*

COMMENT: BASF Corp. 1990l; Reviewer #2 stated: “The document contains only summary tables of a prenatal range-finding toxicity study in rats of glutaraldehyde in drinking water (GD 6–16). An experimental description is missing. Even the strain of rats is not mentioned. As such, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, combined with available experimental details in the introduction of the definitive study (BASF Corp. 1991b), ATSDR considers the available information acceptable and has retained the BASF Corp. (1990l) reference.*

COMMENT: BASF Corp. 1990m; Reviewer #2 stated: “The document contains only summary tables of a prenatal range-finding study in rabbits of glutaraldehyde given by gavage on GD 7–19. An experimental description is missing. Even the strain/source of the test rabbits is not mentioned. As such, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, combined with available experimental details in the introduction of the definitive study (BASF Corp. 1991a), ATSDR considers the available information acceptable and has retained the BASF Corp. (1990m) reference. In addition, Reviewer #3 recommended retaining this report.*

COMMENT: BASF Corp. 1991a; Reviewer # 2 stated: “A detailed GLP-conform study on prenatal toxicity in Himalayan rabbits of glutaraldehyde given by gavage. Performance of experimentation and documentation are state-of-the-art (performed 1990). Clear general toxicity effects of dams at 45 mg/kg per day (GD 7–19), but not at 15 mg/kg. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The BASF Corp. (1991a) reference was retained.*

COMMENT: BASF Corp. 1991b; Reviewer # 2 stated: “A detailed GLP-conform study on prenatal toxicity in Wistar rats of glutaraldehyde given by drinking water (GD 6–16). Performance of experimentation and documentation are state-of-the-art (performed 1991). Minimal effects on dams (impaired water consumption) in test group 2 (250 ppm – 26 mg/kg), clear effect on dams in test group 3 (750 ppm – 68 mg/kg). Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The BASF Corp. (1991b) reference was retained.*

COMMENT: BASF Corp. 1991c; Reviewer # 2 stated: “Brief information on prenatal range-finding toxicity studies in rabbits on drinking water application of glutaraldehyde. No detailed information on experimental details. No information on the strain of rabbits. Therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, combined with available experimental details in the introduction of the definitive study (BASF Corp. 1991a), ATSDR considers the available information acceptable and has retained the BASF Corp. (1991c) reference.*

COMMENT: Confidential 1974; Reviewer #2 stated: “Hypersensitivity testing (Buehler test) in Guinea pigs of glutaraldehyde, performed 1974. It is said the compound produced no reaction. The copy is barely readable. Therefore, details of the study cannot be checked. This means that the study, as reported, is not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. Reviewer #1 indicated that no conclusions were possible. Reviewer #3 suggested to delete the study. Therefore, the study was deleted.*

COMMENT: Confidential 1987a; Reviewer #2 stated: “GLP-conform rat bone marrow cytogenicity study. No chromosomal aberrations were found in bone marrow of male and female SD rats, after single or 5 daily doses of glutaraldehyde (3 different dilutions). Cyclophosphamide was used as positive control. The study is reliable without restrictions (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Confidential (1987a) reference was retained.*

COMMENT: Confidential 1987b; Reviewer #2 stated: “Alcaline elution assay (performed 1986/87) with DNA from testes of SD rats. This type of test was usual at that time, primarily as a research tool, in order to check for DNA cross-links. High dose = MTD, low dose = 1/3 MTD. Test compound: 50% glutaraldehyde solution. Isolated testes DNA was subject to radiation to induce strand brakes before applying the alkaline elution procedure; use of TEM as positive control. Sufficient experimental details, and a deviation from the standard protocol (Kohn/Bradley, 1980/1981) is clearly explained. No DNA-crosslinks were induced. Non-GLP study, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Confidential (1987b) reference was retained.*

COMMENT: Confidential 1987c; Reviewer #2 stated: “An addition to the above study # 14, with a similar protocol, but looking for DNA strand breaks induced by the test substance (without radiation of the samples). Methyl methane sulfonate (MMS) was used as positive control. No DNA strand breaks were observed. Non-GLP-study, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Confidential (1987c) reference was retained.*

COMMENT: Confidential 1991; Reviewer #2 stated: “Magnusson-Kligman Guinea pig maximization test, showing no sensitization effects. Just a summary table, without sufficient experimental documentation. Therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Confidential (1991) reference was deleted from the toxicological profile.*

COMMENT: Confidential 2002; Reviewer #2 stated: “A summary table of larynx and trachea effects after 24 months glutaraldehyde given in drinking water (0, 100, 500, 2000 ppm). The data appear relevant, but cannot be evaluated because the documentation of the study is missing here. Therefore not assignable (class 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, ATSDR considers the information adequate in conjunction with additional information available in a robust summary of the study provided in the BASF (2013) reference. Reviewer #1 indicated that no conclusion is possible. Reviewer #3 did not indicate that the study should be deleted.*

COMMENT: Hoechst Celanese Corp. 1981; Reviewer #2 stated: “Four-hours inhalation study in SD rats at 320 mg/m³ (measured concentration), with no mortality observed. The study dates 1981 (pre-GLP). The report includes all necessary details, comparable to a guideline method. However, there is a difference between nominal and measured airborne glutaraldehyde concentration by a factor of more than 2, and analysis was done just by gravimetry after absorption on the air sample on a charcoal filter. That was acceptable at the time of the study, but nowadays acceptability of this procedure would be limited. In total, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Hoechst Celanese Corp. (1981) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991aa; Reviewer #2 stated: “GLP-conform cutaneous LD₅₀ study of the finished product ‘UCARCIDE antimicrobial 145LT’ showing that the dermal LD₅₀ was beyond 2000 mg/kg. The glutaraldehyde content of the test product is not mentioned, so that it is not clear whether the results are related to glutaraldehyde or the finished product. Therefore, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, the test substance was identified as 45% glutaraldehyde in aqueous solution. The data are considered adequate and ATSDR has retained the Union Carbide Chem & Plas Co. (1991aa) reference. Also, Reviewer #3 indicated that this report should be retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991b; Reviewer #2 stated: “An internal interim progress report on an inhalational LD₅₀ study with a few compounds including ‘25% glutaraldehyde’. No experimental details given; no documentation at all. Therefore not reliable (class 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Union Carbide Chem & Plas Co. (1991b) reference was deleted.*

COMMENT: Union Carbide Chem & Plas Co. 1991bb; Reviewer #2 stated: “GLP-conform skin irritancy testing with the finished product ‘UCARCIDE antimicrobial 145 LT’. Standard procedure, but the glutaraldehyde contents of the test product are not mentioned. Therefore, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, the test substance was identified as 45% aqueous glutaraldehyde. The data are considered adequate and ATSDR has retained the Union Carbide Chem & Plas Co. (1991bb) reference.*

COMMENT: Union Carbide Chem & Plas Co. 1991cc; Reviewer #2 stated: “GLP-conform eye irritancy study with ‘UCARCIDE antimicrobial 145LT’, showing severe effects. Standard procedure, but the glutaraldehyde contents of the test product are not mentioned. Therefore, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, the test substance was identified as 50% glutaraldehyde. The data are considered adequate and ATSDR has retained the Union Carbide Chem & Plas Co. (1991cc) reference.*

COMMENT: Union Carbide Chem & Plas Co. 1991dd; Reviewer #2 stated: “Note: The GLP Compliance Statement and the Quality Assurance Summary Statement (pages 10/11) are missing from the copy provided. Beagle dogs (2/sex/group) received glutaraldehyde in the drinking water or by gavage. The result was that repetitive gavage dosing was not feasible for further testing and that 250 ppm in drinking water could be used for further subchronic toxicity testing as maximal dose. The document contains a description of the experiments and summary tables. As a dose finding/feasibility study, this is reliable without restriction (code 1), provided that the original document contains the GLP Compliance Statement and the Quality Assurance Summary Statement.”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991dd) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991e; Reviewer #2 stated: “Brief summary of results from earlier (pre-GLP, dated 1975) acute oral and dermal LD50 studies, lethality from inhalation of substantially saturated vapors, and dermal and ocular irritation studies. Insufficient experimental details, therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Union Carbide Chem & Plas Co. (1991e) reference was deleted because the composition of test substance was not specified.*

COMMENT: Union Carbide Chem & Plas Co. 1991ee; Reviewer #2 stated: “A 90-day drinking water study in dogs with 4 doses (plus control group). Local effects (vomiting) occurred in the medium and high dose groups, likely as a sign of acute local irritation. Study dates 1990; no GLP statement included, but parameters of the study are closely related/comparable to a guideline method. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991ee) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991f; Reviewer #2 stated: “A 4-day drinking water study of glutaraldehyde in Wister rats dating 1976 (pre-GLP) of dose/range-finding character. The procedures are described in detail, including analysis (stability check) of the testing material. Acceptable as a dose finding study, and as such closely related/comparable to a guideline method. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991f) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991ff; Reviewer #2 stated: “The study, dating 1981, looks at the excretion routes of the 14C label of 1,5-14C-glutaraldehyde administered to male F344 rats by gavage. High proportions of the label were excreted in the feces (35%) and expired as 14CO2 (21%). Urinary elimination was just 6.4%. Studies of this kind were usual at the time of the study performance. Nowadays, one would expect detailed analytical data. The investigations described cannot be subsumed under a testing guideline, but are nevertheless well documented and scientifically acceptable. Thus, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991ff) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991gg; Reviewer #2 stated: “By 1980, in vitro mutagenicity testing was performed using standard procedures, applying the CHO cell mutation test, SCE and UDS tests. This was standard at the time of test performance. Glutaraldehyde displayed no specific mutagenicity in these tests. However, the data for selection of test concentrations are not included in the tables. Thus, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991gg) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991hh; Reviewer #2 stated: “Addition to the tests described in Project report 43-16 regarding the CHO mutation testing, but with a lower concentration range. Glutaraldehyde displayed no specific mutagenicity in these tests. As in report 43-16, the data for selection of test concentrations are not included in the tables. Thus, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991hh) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991ii; Reviewer #2 stated: “Standard Ames assay with and without S9 following standard protocols, but only with one *S. typhimurium* strain (TA100). No mutagenicity found. For TA100, reliable without restrictions (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991ii) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991jj; Reviewer #2 stated: “Chromosomal aberration assay in CHO cells in vitro with TEM as positive control. Standard procedures (GLP-conform) were used. Extensive description of the experiments. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991jj) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991k; Reviewer #2 stated: “Dermal LD50 and ocular irritation studies. The reporting is not very detailed. Specifically, for eye irritation results (rabbit) the score tables I and II are missing from the report! In total, reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991k) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991l; Reviewer #2 stated: “Summary report of acute oral LD50 studies of various dilutions of glutaraldehyde. The relevant result from this overview is that LD50 values based on standard test procedures for the 50, 25 and 10% dilutions were similar, and for higher dilutions (5 and 1%) considerably higher. Data are conclusively summarized in tables. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991l) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991m; Reviewer #2 stated: “Acute dermal and ocular irritation studies based on standard procedures. As such, the studies appear to be in order. However, all result tables are missing. Therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability, although tables are missing. The Union Carbide Chem & Plas Co. (1991m) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991o; Reviewer #2 stated: “14-day oral drinking water study. The descriptions are o.k. However, all result tables and appendices are missing from my file. Therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability, although tables are missing. The Union Carbide Chem & Plas Co. (1991o) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991p; Reviewer #2 stated: “An acute inhalation toxicity study at single dynamically-generated vapor concentration (8.1 ppm); the 4-hr LC50 was apparently higher than the test concentration. The methodology and procedures are adequately described in detail, comparable to a guideline method. The methodology of analysis of the atmosphere was standard at the time of performance of the study (1985). In total, reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991p) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991q; Reviewer #2 stated: “Results of acute dermal toxicity studies (dated 1985) with 10, 15 and 45% glutaraldehyde solution. Result tables are provided, but a detailed method description is missing, as the ‘attached standard test procedure section’ is missing. Therefore reliable with restrictions (code 2).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991q) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991r; Reviewer #2 stated: “Subchronic drinking water study (controls, 50, 250, 1000 ppm) in F344 rats (1985). The mid- and high-dose caused decreased water consumption (probably due to a bad irritant taste of the drinking water). No other pathological findings. GLP-conform study with sufficient description of methodology details and results. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991r) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991s; Reviewer #2 stated: “LD50 study in SD rats of ‘UCARCIDE instrument sterilant 602’. The doses are given in ‘ml/kg’, without mentioning the dilution of glutaraldehyde in the tested product. Therefore not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Union Carbide Chem & Plas Co. (1991s) reference was deleted.*

COMMENT: Union Carbide Chem & Plas Co. 1991t; Reviewer #2 stated: “LD50 study in SD rats of ‘UCARCIDE 145 LT’. The doses are given in ‘ml/kg’, without mentioning the dilution of glutaraldehyde in the tested product. Therefore not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, the test substance was identified as 45% glutaraldehyde and mL/kg can readily be converted to mg/kg. The data are considered adequate and ATSDR has retained the Union Carbide Chem & Plas Co. (1991t) reference. Also, Reviewer #1 agrees that the study is adequate and Reviewer #3 did not specify this study as one to be deleted.*

COMMENT: Union Carbide Chem & Plas Co. 1991v; Reviewer #2 stated: “14-day oral toxicity study in CD-1 mice in drinking water (groups: controls, 100, 250, 1000 ppm). GLP-conform study with sufficient description of methodological details and results. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991v) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991w; Reviewer #2 stated: “90-day oral toxicity study in CD-1 mice in drinking water (groups: controls, 100, 250, 1000 ppm). GLP-conform study with

sufficient description of methodological details and results. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991w) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991x; Reviewer #2 stated: “Acute inhalation (4 h) toxicity studies in SD rats using 3 exposure levels of glutaraldehyde; clinical signs were seen pointing to local irritancy, and no deaths occurred. GLP-conform study with sufficient description of methodological details and results. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991x) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991y; Reviewer #2 stated: “Subacute (2 weeks) dermal toxicity study designed as a dose finding study for a later chronic dermal study of glutaraldehyde. Guideline-conform study with sufficient description of methodology and tabular presentation of results. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1991y) reference was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991z; Reviewer #2 stated: “Acute oral LD50 study in SD rats. The study was performed according to GLP. However, the doses testes and results given are entirely related to the finished product ‘UCARCIDE antimicrobial 145LT’. The contents of glutaraldehyde in this product are not mentioned in the report. Therefore not reliable (code 3), because of insufficient documentation.”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, the test substance was identified as 45% aqueous glutaraldehyde. The data are considered adequate and ATSDR has retained the Union Carbide Chem & Plas Co. (1991z) reference. Also, Reviewer #1 agrees that the study is adequate and Reviewer #3 did not specify this study as one to be deleted.*

COMMENT: Union Carbide Chem & Plas Co. 1992; Reviewer #2 stated: “Oral LD50 study in SD rats with UCARCIDE antimicrobial 250, containing 50% glutaraldehyde. GLP-conform study; procedure and results (in tables) are described in a sufficiently detailed manner. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Chem & Plas Co. (1992) reference was retained.*

COMMENT: Union Carbide Corp. 1966; Reviewer #2 stated: “Patch test with human volunteers with 5% glutaraldehyde, dated 1966. The procedure is described in detail, comparable to a guideline method, and the results (details shown in tables) are critically discussed as to the statistical methodological limitations. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer's assessment as indication of acceptability. The Union Carbide Corp. (1966) reference was retained.*

COMMENT: Union Carbide Corp. 1976; Reviewer #2 stated: "Memo of an early (1976) human sensory irritation threshold study with glutaraldehyde vapor. The procedure description does not give sufficient experimental details, and the results are not described in a sufficient manner, therefore not assignable (code 4)."

RESPONSE: *ATSDR interprets the Reviewer's assessment as indication of unreliability. However, ATSDR considers the information adequate to determine a sensory irritation threshold. The Union Carbide Corp. (1976) reference was retained.*

COMMENT: Union Carbide Corp. 1980; Reviewer #2 stated: "Repeated insult patch test with 0.1, 0.2 and 0.5 % glutaraldehyde in volunteers (performed 1980); appears adequate. Experimental procedure and results are clearly described, comparable to a guideline method. Reliable without restriction (code 1)."

RESPONSE: *ATSDR interprets the Reviewer's assessment as indication of acceptability. The Union Carbide Corp. (1980) reference was retained.*

COMMENT: Union Carbide Corp. 1992a; Reviewer #2 stated: "Early (1964) acute oral (rat) and dermal (rabbit) LD50 studies, acute inhalation study using 'saturated vapor concentration', acute dermal and ocular irritation studies, using 45% aqueous glutaraldehyde test solution. The experimental procedures are described only very briefly. The studies were intended as 'range finding studies' for later experimentation. Results of the '24 h irritation tests' (rabbit eyes) are missing. The very early inhalation study is by far not comparable with modern requirements, and the effective concentration of glutaraldehyde in this experiment is unclear. In total, not reliable (code 3)."

RESPONSE: *ATSDR interprets the Reviewer's assessment as indication of unreliability. However, ATSDR considers the information adequate to identify an acute exposure hazard. In addition, Reviewer #3 indicated that this study should be retained. The Union Carbide Corp. (1992a) reference was retained.*

COMMENT: Union Carbide Corp. 1992b; Reviewer #2 stated: "Very early (1964!) acute oral (rats, gavage) and dermal (rabbits) LD50 studies, plus an acute inhalation study using 'saturated vapor', and acute dermal and ocular irritation studies using 50% aqueous glutaraldehyde. The experimental procedures are described only very briefly. The studies were intended as range finding studies for later experimentation. Results of the '24 h irritation tests' (rabbit eyes) are missing. The very early inhalation study is by far not comparable with modern requirements, and the effective concentration of glutaraldehyde in this experiment is unclear. In total, not reliable (code 3)."

RESPONSE: *ATSDR interprets the Reviewer's assessment as indication of unreliability. However, ATSDR considers the information adequate to identify an acute exposure hazard. In addition, Reviewer #3 indicated that this study should be retained. The Union Carbide Corp. (1992b) reference was retained.*

COMMENT: Union Carbide Corp. 1992c; Reviewer #2 stated: “Acute oral and dermal LD50 ‘range finding toxicity’ studies with 25% glutaraldehyde, plus acute inhalation study using saturated vapor concentration, and acute dermal and ocular irritation studies using 25% aqueous glutaraldehyde test solution. Irritancy data are not given in detail. As in Reports 27-137 and 40-50 (above), the inhalation study is by far not comparable with modern requirements. Specifically, the effective concentration of glutaraldehyde in this experiment is unclear. In total, not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, ATSDR considers the information adequate to identify an acute exposure hazard. In addition, Reviewer #3 indicated that this study should be retained. The Union Carbide Corp. (1992c) reference was retained.*

COMMENT: Union Carbide Corp. 1992d; Reviewer #2 stated: “Repeated-exposure inhalation toxicity study (9 exposures) with 0, 0.3, 1.1 and 3.1 ppm glutaraldehyde. The description in the text is adequate, and the study appears reliable as such. However, all Tables and Appendices showing the detailed results are missing from this file. Therefore, it cannot be evaluated: not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. ATSDR considers the information adequate in the absence of data tables. The Union Carbide Corp. (1992d) reference was retained.*

COMMENT: Union Carbide Corp. 1992e; Reviewer #2 stated: “Repeated-exposure inhalation toxicity study (9 exposures) with 0, 0.2, 0.6, and 2.09 ppm glutaraldehyde. The description in the text is adequate, comparable to a guideline method, and the study appears reliable as such. By contrast to Report 46-63, detailed results tables are included. Therefore reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Corp. (1992e) reference was retained.*

COMMENT: Union Carbide Corp. 1992f; Reviewer #2 stated: “Subchronic (14-week) repeated-exposure inhalation toxicity in F344 rats (6 h every day) at 0, 20.3, 94.3 and 194.2 ppb glutaraldehyde according to standard procedures, showing signs of local irritation at the 2 higher concentrations. This would be an important study for assessment of glutaraldehyde toxicity. However, there are no result tables in the file. Thus, it is a pity that the study is not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. ATSDR considers the information adequate in the absence of data tables. The Union Carbide Corp. (1992f) reference was retained.*

COMMENT: Union Carbide Corp. 1992g; Reviewer #2 stated: “This is an acute 6-hour inhalation toxicity study in Wistar rats using a ‘saturated vapor’ atmosphere from a 30% glutaraldehyde solution. During this single exposure, the concentration dropped from 11 to 2 ppm glutaraldehyde! Therefore difficult to evaluate: not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Union Carbide Corp. (1992g) reference was deleted.*

COMMENT: Union Carbide Corp. 1992h; Reviewer #2 stated: “Guideline-conform acute (60 min and 4-hour) dermal irritation study in NZ rabbits with 50% glutaraldehyde using single dose. Repeated irritation score reading for up to 7 days. Results are completely presented in tables. Reliable without restriction (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Corp. (1992h) reference was retained.*

COMMENT: Union Carbide Corp. 1992i; Reviewer #2 stated: “Acute oral LD50 studies of 0.01, 0.05, 0.1, 1.0, 5.0, 25 and 50% glutaraldehyde. The detailed results are presented in tabular form. However, as far as methodology is concerned, in the ‘Procedures’ section it says: ‘Description of the test procedures are included in the attached standard test procedures section (Appendix 1)’. Regrettably, this appendix that describes the methodology is missing from this file. Thus, even the strain of mice remains unclear! Therefore not assignable (code 4).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. However, ATSDR considers the information adequate. In addition Reviewer #1 and Reviewer #3 consider this report acceptable. The Union Carbide Corp. (1992i) reference was retained.*

COMMENT: Union Carbide Corp. 1992j; Reviewer #2 stated: “Acute (1-hour) dermal irritation study with 50% glutaraldehyde in NZ rabbits, according standard test procedures. Reportings of methodology (appendix 1) and results are complete. Reliable without restrictions (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Corp. (1992j) reference was retained.*

COMMENT: Union Carbide Corp. 1992k; Reviewer #2 stated: “Acute (6-hour) inhalation exposure of female F344 rats to ‘saturated vapor’ generated from a 50% glutaraldehyde solution. Two different methods of exposure analysis (Tenax trapping and GC) gave conflicting results by a factor of 10! It is said that the GC data ‘may have been incorrect’, without providing further explanation. Therefore not reliable (code 3).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of unreliability. The Union Carbide Corp. (1992k) reference was deleted.*

COMMENT: Union Carbide Corp. 1992l; Reviewer #2 stated: “Acute (4-hour) LC50 studies in F344 rats exposed to glutaraldehyde vapor at target concentrations 0, 10, 20 or 50 ppm. Two analytical methods for chamber glutaraldehyde gave consistent results. The toxicity data are different compared to other studies, which is well discussed in the text. Reporting is complete. Any exception to the standard protocol is described. Reliable without restrictions (code 1).”

RESPONSE: *ATSDR interprets the Reviewer’s assessment as indication of acceptability. The Union Carbide Corp. (1992l) reference was retained.*

COMMENT: Union Carbide Corp. 1993a; Reviewer #2 stated: “These are GLP-conform in vivo genotoxicity studies (chromosomal aberrations in bone marrow from treated SD rats) on a 50% glutaraldehyde product. However, all result tables are missing from the file. Therefore, not assignable (code 4).”

RESPONSE: *Union Carbide Corp. 1993a was deleted; Vergnes and Ballantyne (2002) was retained as the source of information for the unpublished study.*

COMMENT: Union Carbide Corp. 1993b; Reviewer #2 stated: “Note: The file ‘UnionCarbideCorp_1993b’ that I received is identical to the file ‘UnionCarbideCorp_1993a’ and contains the rat chromosomal aberration study. I did not receive the file of a mouse micronucleus study!”

RESPONSE: *Union Carbide Corp. 1993b was deleted; Vergnes and Ballantyne (2002) was retained as the source of information for the unpublished study.*

COMMENT: Union Carbide Corp. 1996; Reviewer #2 stated: “Note: This file is the same as Union Carbide Corp. 1976 (#48 of this list).”

RESPONSE: *The noted duplication was corrected; the Union Carbide Corp. (1996) reference was deleted.*

Comments provided by Reviewer #3:

Reviewer #3 submitted an electronic file that contained comments on selected portions of each chapter of the Toxicological Profile for Glutaraldehyde.

Chapter 1: Public Health Statement

COMMENT: Reviewer #3 stated: “The paragraph discussing glutaraldehyde and cancer should be changed. It should be stated that there is no scientific evidence that glutaraldehyde is carcinogenic in animals or humans.”

RESPONSE: *The suggested statement is made in paragraph 4 of this section; therefore, no additional statement is necessary.*

Chapter 2: Relevance to Public Health

COMMENT: Reviewer #3 stated: “The statement that glutaraldehyde can contaminate food sources following spraying of poultry houses has no basis. In fact the EPA states that ‘the Agency has no concerns for the agricultural uses listed’ hence this sentence should be struck from the document.”

RESPONSE: *The sentence in question was changed to read “A slight potential for glutaraldehyde residues to contaminate food sources exists, as it is used as a disinfectant for poultry/livestock equipment and processing premises in animal housing (EPA 2007).” This is in line with text from EPA (2007).*

COMMENT: Reviewer #3 stated: “The information on metabolism in animals is scant and is absent in humans as very few studies have evaluated the toxicokinetics in animals and none in humans. Some effects in animals are of little or no concern to humans e.g. exposure via intubation of glutaraldehyde or via injection. Evaluation of exposure to humans via contamination of endoscopy should be mentioned in this section (see later).”

RESPONSE: *Text was added to note implication of glutaraldehyde as a cause of colitis and diarrhea following endoscopy or sigmoidoscopy procedures.*

COMMENT: Reviewer #3 stated: “Doses of exposure (50, 250, 1000 ppm) on page 10 when referencing van Miller et al. (2002) need to be included in the text.”

RESPONSE: *Exposure concentrations were added.*

Chapter 3: Health Effects

Route of Exposure

COMMENT: Reviewer #3 stated: “Adding a subheading of Human Studies and a subheading Animal Studies for each section of the routes of exposure would be helpful.”

RESPONSE: For each heading in Section 3.2, ATSDR convention is to discuss human data first when available, followed by animal data. The addition of subheadings does not appear necessary.

COMMENT: Reviewer #3 stated: “In sections where no human studies have been reported, the profile should include a sentence stating this before discussing animal effects.”

RESPONSE: The toxicological profile follows the suggested convention. For systemic effects, statements are made up front regarding types of effects in humans and/or animals for which data were not located. No change was made to the convention used by ATSDR for toxicological profiles.

3.2.1 Inhalation Exposure

COMMENT: Reviewer #3 stated: “The conclusions in the text relating to human studies were well tabulated in table 3-2. It would be appropriate to state the occupational exposure limits i.e. the TLV (0.05ppm), ceiling TWA (0.02ppm) and life threatening concentration (5ppm) on Page 19 in the text where Table 8-1 is referenced. Thus if the reader consults Table 3-2 they can see that the concentrations in the studies listed were usually lower than the regulations and guidelines.”

RESPONSE: Addition of regulatory and guideline data to LSE Tables is beyond the scope of the intended purpose of the tables. The regulatory and guideline data are available in Table 8-1.

COMMENT: Reviewer #3 stated: “The paragraph on page 25 discussing the results of the carcinogenic studies should be moved to page 32 under 3.2.1.7 Cancer.”

RESPONSE: The data on page 25 describe non-neoplastic lesions in the respiratory tract and are therefore presented in Section 3.2.1.2 (Respiratory Effects). The suggested move was not made.

3.2.2 Oral Exposure

COMMENT: Reviewer #3 stated: “No changes required except changes in the text as shown in the submission of the profile.”

RESPONSE: Suggested changes on annotated pages are addressed in the section of this formal disposition that identifies specific comments made by Reviewer #3.

3.2.3 Dermal Exposure

COMMENT: Reviewer #3 stated: “No changes suggested.”

RESPONSE: No response necessary.

Quality of Human Studies

COMMENT: Reviewer #3 stated: “Only a few human studies were identified in the text because few studies have been published. Appropriate NOAEL’s and LOAEL’s were identified for studies with the

appropriate data in table 3-1 which summarized the data succinctly. The conclusions of the human studies were appropriate and well described in the profile. One of the concerns is the pharmacodynamics of glutaraldehyde and the degradation pathway in both humans and animals. Very little was discussed of the pathway in either human or animal studies as very little is known of the pathway. This is an area for further study.”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “Ocular exposure in humans was basically discounted, as some of the ocular irritation was self-reported. I believe this is of importance as many health workers are exposed to glutaraldehyde while cleaning surgical instruments. This is an area where more studies could be done to assess the actual concentration that elicits ocular irritation. (Page 28). Waldron reported that 150 hospital workers exposed to glutaraldehyde complained of ocular irritation (page 30).”

RESPONSE: *Waldron (1992) was added to the list of citations for ocular effects and the following sentences were added to the text: “In some occupational reports that included measurements of personal and/or workplace airborne glutaraldehyde levels, ocular irritation was self-reported at short-term exposure levels as low as 0.05–0.2 ppm. However, these reports do not provide adequate exposure-response data for useful quantitative risk analysis.”*

General Population and Occupational Exposure

COMMENT: Reviewer #3 stated: “There is no mention of the possibility that patients undergoing exploratory surgery could be exposed to glutaraldehyde by an endoscopy tube that has not been carefully washed with sterile water. This is unlikely but it has occurred and publications are in the literature. The following references describe a few of the studies that have been published on this topic that were omitted from the profile and their inclusion should be considered.

Nelson DB. 2003. Infectious disease complications of GI endoscopy: Part II, exogenous infections: Gastrointestinal Endoscopy 57:695-711.

Stein BL, Lamoureux E, Miller M, et al. 2001. Glutaraldehyde-induced colitis. Canadian Journal of Surgery 44(2):113-116.

Takigawa T, Endo Y. 2006. Effects of glutaraldehyde exposure on human health. J Occup Health 48:75-87.

West AB, Kuan S-F, Bennick M, et al. 1995. Glutaraldehyde colitis following endoscopy: Clinical and pathological features and investigation of an outbreak. Gastroenterology 108:1250-1255.”

RESPONSE: *A discussion regarding potential hazard of exposure to glutaraldehyde during endoscopy or sigmoidoscopy procedures was added to Section 6.5. Nelson (2003) and Takigawa and Endo (2006) are reviews and are not considered necessary additions to the toxicological profile. The studies of Stein et al. (2001) and West et al. (1995) were already cited in the profile.*

Quality of Animal Studies

COMMENT: Reviewer #3 stated: “For the most part the animal studies identified in the text were performed following good animal practices. The species used for the drinking water studies and dermal application of glutaraldehyde was appropriate. In some unpublished studies, the lack of controls, use of only a few animals and statistical evaluation of the data was discounted for various reasons by the writers of the profile. Inclusion of a list of these studies in Table B-16 is helpful.”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “I have a concern regarding the stability of diluted glutaraldehyde in drinking water studies where animals are on the regimen for 7-14 days or longer. In some cases the glutaraldehyde solution was left in the water bottles for a week or longer at room temperature. There are indications that glutaraldehyde decomposes after four days. There is also evidence that glutaraldehyde may be more toxic at lower dilutions. Is this because other by-products are formed if the solution is exposed to light or kept at room temperature? There is no indication why this is a problem. In the study reported in Union Carbide (1991w), it is stated that the glutaraldehyde solution is stable for 14 days. However, no data is presented to substantiate that claim.”

RESPONSE: *According to van Miller et al. (2002), stability tests indicated stability up to 21 days for 50 and 1,000 ppm solutions. No data were located to suggest that toxicity associated with acute-duration exposure to glutaraldehyde might be the result of byproducts formed in solutions exposed to light or kept at room temperature. Text was added to the profile in Section 3.2.2.1 to note that the apparent increasing lethality with decreasing glutaraldehyde concentration (increasing dosing volume to achieve dilution) has not been explained, but indicates that water should not be used to dilute ingested glutaraldehyde.*

COMMENT: Reviewer #3 stated: “Within the text on page 35, the authors should discuss the different LD50’s obtained in both rats and mice depending on whether the concentrated glutaraldehyde was diluted and the same volume given to the animals by intubation or whether different volumes of the undiluted glutaraldehyde were given by intubation. Apparently the LD50 obtained via these two methods are different and it appears that the amount of water in the solution given to the animals has an effect on the LD50. Is there an explanation for this? Perhaps the authors should speculate on this observation?”

RESPONSE: *Text was added to note that dosing volume varied.*

Toxicity of acidic and alkaline glutaraldehyde

COMMENT: Reviewer #3 stated: “Virtually all the animal studies have tested glutaraldehyde at an acidic pH; the form in which it exists and is usually used. However, the glutaraldehyde used in sterilizing endoscopes and other medical equipment has been alkalized by raising the pH to above 7. It would be important to know whether glutaraldehyde tested at an alkaline pH would have the same effects as found for glutaraldehyde at an acidic pH. Such a study might be difficult due to the low stability of glutaraldehyde in alkaline conditions. One preliminary study in humans (Union Carbide Corp. 1996) reported no differences between the irritation thresholds for alkaline or acidic glutaraldehyde, but this study lacked a detailed depiction of the results. A reference to Figures 1 and 2 and Table 2 was mentioned but not provided. It is not clear what concentration of glutaraldehyde was used. Hence a further study in humans as well as animals should be undertaken.”

RESPONSE: *Results from an acute oral lethality study were added to demonstrate that oral administration of buffered (relatively alkaline or neutral pH) and unbuffered (acidic) solutions of glutaraldehyde resulted in similar LD₅₀ values in male and female rats.*

COMMENT: Reviewer #3 stated: “The conclusions drawn by the authors for most of the studies were appropriate. The statistical tests used to analyze the data in the profile are appropriate.”

RESPONSE: *No response necessary.*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: Reviewer #3 stated: “The LSE tables and figures are complete and self-explanatory. They were helpful in obtaining a snapshot of the studies in the profile. I did indicate the same error in three of the tables (see below) in Appendix B.”

RESPONSE: *The errors in tables of Appendix B were corrected.*

COMMENT: Reviewer #3 stated: “I think the categorization of ‘less serious’ and ‘serious’ for the effects in the LSE tables are appropriate. Those MRL’s that have been calculated are appropriate and where no MRL has been derived, the data does not support such a derivation.”

RESPONSE: *No response necessary.*

Evaluation of Text

COMMENT: Reviewer #3 stated: “In many cases the limitations of the studies have been adequately and accurately discussed. However, the number of human studies is very small and hence exposure of humans has been difficult to assess.

The acute dermal exposure study cited in Union Carbide Corp. (1966) was one of the few human studies. The experimental design was very complicated with changes being made as the study progressed. It appeared that glutaraldehyde was not the reason for most of the responses recorded in the study but rather a plaster made by 3M used to hold the discs saturated with glutaraldehyde. There was no control group nor were any statistical analyses performed. Although this was a really poor study design I suggest it remain in the profile due to the paucity of human studies.

The second study evaluating dermal sensitivity in humans (Union Carbide Corp. 1980) was also poorly designed with no control group or statistical analyses. However, a small percentage of positive responses were seen and hence the study should remain in the profile.”

RESPONSE: *ATSDR agrees.*

COMMENT: Reviewer #3 stated: “There has been very little discussion of dose response relationships in humans but LD₅₀’s were discussed for many of the animal studies.

The animal data has not been used to draw support for the human effects.”

RESPONSE: *No response necessary*

3.3 Genotoxicity

COMMENT: Reviewer #3 stated: “The genotoxicity studies were well described and the results in the text indicated that glutaraldehyde was positive in a number of in vitro assays but results in vivo were mostly negative with only one of the seven assays indicating a positive result and one an equivocal outcome. I suggest a summary statement such as the one mentioned here be added to the end of the section on genotoxicity to sum up the findings.”

RESPONSE: *The summary paragraph was revised to quantify the numbers of studies that reported negative, positive, and weakly positive results in vivo.*

3.4 Toxicokinetics

COMMENT: Reviewer #3 stated: “Only a few studies have been performed on animals and none in humans on the toxicokinetics of glutaraldehyde. It might be useful to add a concluding sentence stating that depending on the mode of administration of radiolabeled glutaraldehyde the proportion of radioactivity found in various tissues and urine and feces was different. Since no identification of possible metabolites was performed in any of these studies the metabolism of glutaraldehyde in various tissues could not be determined.”

RESPONSE: *At the beginning of Sections 3.4.2 and 3.4.4, a sentence was added to note that in animal studies that involved administration of radiolabeled glutaraldehyde, the proportion of activity in various tissues (Section 3.4.2) and urine and feces (Section 3.4.4) varied according to route of exposure.*

3.5 Mechanisms of Action

COMMENT: Reviewer #3 stated: “No additional comments.”

RESPONSE: *No response necessary.*

3.6 Hazard identification and Minimal Risk Levels

COMMENT: Reviewer #3 stated: “No additional comments.”

RESPONSE: *No response necessary.*

3.7 Toxicities Mediated Through the Neuroendocrine Axis

COMMENT: Reviewer #3 stated: “No additional comments.”

RESPONSE: *No response necessary.*

3.8 Children's Susceptibility

COMMENT: Reviewer #3 stated: "No additional comments."

RESPONSE: *No response necessary.*

3.9 Biomarkers of Exposure and Effect

COMMENT: Reviewer #3 stated: "No additional comments."

RESPONSE: *No response necessary.*

3.10 Interactions with Other Chemicals

COMMENT: Reviewer #3 stated: "No information is available."

RESPONSE: *No response necessary.*

3.11 Populations that are usually susceptible

COMMENT: Reviewer #3 stated: "Scant information on this possibility."

RESPONSE: *No response necessary.*

3.12 Methods for Reducing Toxic Effects

COMMENT: Reviewer #3 stated: "This section was clear and no changes are suggested."

RESPONSE: *No response necessary.*

3.13 Adequacy of the Data Base

Existing Information of Health Effects

COMMENT: Reviewer #3 stated: "Under the section of quality of human data, I listed three references not cited in the profile that will provide additional information on human studies that I suggest be added to the profile."

RESPONSE: *Reviewer #3 actually listed 4 references (Nelson 2003); Stein et al. 2001; Takigawa and Endo 2006; and West et al. 1995). Two of these studies were already in the profile (Stein et al. 2001; West et al. 1995); the other 2 reports (Nelson 2003; Takigawa and Endo 2006) are reviews that do not provide information not available from primary sources; therefore, they were not added to the tox profile.*

Identification of Data Needs

COMMENT: Reviewer #3 stated: “The text is not biased.

I agree that additional animal studies are needed to quantitatively assess the sub-lethal acute oral toxicity in the most sensitive animal species to derive an acute duration oral MRL for glutaraldehyde.

In addition, I agree that glutaraldehyde-exposed humans should be monitored for nasal lesions, dermal sensitization and respiratory sensitization as suggested in the profile (page 90).”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “An intermediate duration dermal toxicity study in animals is needed.”

RESPONSE: *ATSDR agrees, as noted in the toxicological profile.*

COMMENT: Reviewer #3 stated: “Although a chronic inhalation study of glutaraldehyde in rats and mice (NTP, 1999) did not indicate carcinogenic activity, it was suggested in the profile that a study of chronic oral exposure (via drinking water) be undertaken. I would agree with this suggestion as the study in Wistar rats (Confidential, 2002) cited in the profile lacked many details. The authors use the term metaplasma in the table when they mean metaplasia. This study suggested that glutaraldehyde might be carcinogenic in Wistar rats. Thus, a 2-year bioassay of glutaraldehyde in drinking water in F344 rats and B6C3F1 mice, the usual strains for a bioassay, should be undertaken.”

RESPONSE: *ATSDR agrees, as noted in the toxicological profile.*

COMMENT: Reviewer #3 stated: “Although the profile suggests that an in vivo mutagenicity assay is needed, it would depend on which assay is selected. Of those in vivo assays for which some data is available, only the chromosomal aberrations or micronucleus formation would be worth considering. Another possibility would be to use a Big Blue mouse or similar system as an in vivo model.”

RESPONSE: *A statement was added to note a need for additional studies to support or refute evidence for glutaraldehyde-induced chromosomal aberrations and micronuclei in mouse bone marrow cells in vivo.*

COMMENT: Reviewer #3 stated: “I would agree that additional human and animal studies to evaluate hypersensitivity would be useful and informative. At the same time the exposed humans and animals could be evaluated for nasal lesions.”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “The writers of the profile suggest more in-depth pharmacodynamic studies in animals. I agree that very little is known of the pharmacokinetics of glutaraldehyde including the tissue in which intermediates are formed, the rate of excretion and identification of the metabolites

found in the urine and feces. It would be interesting to undertake these studies with glutaraldehyde under acidic and alkaline pH.”

RESPONSE: *No response necessary.*

Chapters 4 and 5

COMMENT: Reviewer #3 stated: “No changes are necessary in the chemical and physical information or in the chapter on production, use and disposal.”

RESPONSE: *No response necessary.*

Chapter 6 Potential for Human Exposure

COMMENT: Reviewer #3 stated: “The profile does trace glutaraldehyde from its points of release into various parts of the environment and explains its rate of degradation and potential exposure to the population. I do not know of any other relevant information regarding its transformation in the environment that needs to be added. The profile adequately describes sources and pathways of exposure involved in the populations handling glutaraldehyde.”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “An intermediate duration dermal toxicity study in animals is needed.”

RESPONSE: *ATSDR agrees, as noted in the toxicological profile.*

Chapter 7: Analytical Methods

COMMENT: Reviewer #3 stated: “I am aware of two methods to measure glutaraldehyde metabolites including glutaric acid. None of these methods were identified in the profile:

Baric, I., Wagner, P., Feyh, M., Liesert, M., Buckel, W. and Hoffmann, G.F. (1999) Sensitivity and specificity of free and total glutaric acid and 3-hydroxyglutaric acid measurements by stable-isotope dilution assays for the diagnosis of glutaric aciduria type 1. *J Inherited Metab Dis* 22:867-882.

Shigematsu, Y., Hata, I., Tanaka, Y., Tajima, G., Sakura, N., Naito, E., Yorifuji, T. (2005) Stable-isotope dilution gas chromatography-mass spectrometric measurement of 3-hydroxyglutaric acid, glutaric acid and related metabolites in body fluids of patients with glutaric aciduria type 1 found in newborn screening. *J Chromatog B* 823:7-12”

RESPONSE: *Both references were added and the method used by Shigematsu et al. (2005) was briefly described.*

Identification of Data Needs

COMMENT: Reviewer #3 stated: “I agree that more research is required to study the metabolism and identification of intermediates in animal tissues to understand how humans and animals metabolize glutaraldehyde.”

RESPONSE: *No response necessary.*

COMMENT: Reviewer #3 stated: “Another study that would be helpful would be the analysis and identification of glutaraldehyde metabolites in the urine of exposed health workers. A few methods that identify glutaric and 3-hydroxyglutaric acids, in human urine have been developed (see above).”

RESPONSE: *The following was added to Section 7.3.1: “Methods are available to detect glutaric acid (a metabolite of glutaraldehyde) in bodily fluids. Such methods could be applied to detect and quantify glutaraldehyde metabolites in urine and/or serum of glutaraldehyde-exposed workers.”*

COMMENT: Reviewer #3 stated: “I agree that no further studies of glutaraldehyde in soil is necessary although it might be interesting to determine the pathway of break down of glutaraldehyde under aerobic and anaerobic conditions in the presence of a representative consortium of bacteria found in the soil.”

RESPONSE: *No response necessary.*

Chapter: 8 Regulations and Advisories

COMMENT: Reviewer #3 stated: “I do not have any additional information.”

RESPONSE: *No response necessary.*

Chapter 9: References

COMMENT: Reviewer #3 stated: “I have a few additional references that might be useful especially for additional studies with glutaraldehyde.”

RESPONSE: *References identified by Reviewer #3 in specific comments on Chapter 7 were: Baric et al. (1999) and Shigematsu et al. (2005) for analytical methods; and Nelson (2003), Stein et al. (2001), Takigawa and Endo (2006), and West et al (1995) for General Population and Occupational Exposure. The references Baric et al. (1999) and Shigematsu et al. (2005) were added. The references Stein et al. (2001) and West et al (1995) were already in the tox profile. The references Nelson (2003) and Takigawa and Endo (2006) are review articles that were not added to the tox profile because they did not contain primary study data.*

Reviewer #3 comments on annotated pages of the toxicological profile

Reviewer #3 submitted an electronic file of the Toxicological Profile for Glutaraldehyde that included tracked changes and embedded comments. Tracked changes and comments that were of sufficient nature

to warrant a formal response are itemized below and identified by page (P) and line (L) on which they are found in the file submitted by Reviewer #3.

Note: *Page and line numbers in this file do not correspond to the page and line numbers in the file of the Toxicological Profile for Glutaraldehyde that was provided to Reviewer #3 due to the use of tracked changes, which included suggested additions and deletions.*

COMMENT: P10, L29: Reviewer #3 stated that a citation is required for the statement “LGLL is a common and highly variable spontaneous neoplasm in F344 rats.”

RESPONSE: *This statement came directly from EPA (2006), which is identified as the source in the first portion of the statement.*

COMMENT: P10, L10: Reviewer #3 indicated that the length of time in the chronic exposure should be added.

RESPONSE: *The term “chronic” was qualified by adding “(≥1 year).”*

COMMENT: P97, L2: Reviewer #3 suggested that BALF should be defined in the list of abbreviations.

RESPONSE: *BALF was added to the list of abbreviations in Appendix D.*

COMMENT: P116, L23: Reviewer #3 suggested changing the term “white water effluent” to “waste water effluent”.

RESPONSE: *“White” water is the correct term; a definition for the term was added to the profile.*

COMMENT: P120, L3: Reviewer #3 asked for concentrations and those of pesticides used to be added to the statement: “Medical equipment and dental equipment, such as endoscopes and operating room instruments, are often disinfected using glutaraldehyde at higher concentrations than used in pesticidal applications (EPA 2007).”

RESPONSE: *The requested addition of concentrations was made.*

Reviewer #3 submitted an additional electronic file that consisted of comments on selected results in Table B-16 of Appendix B

COMMENT: Reviewer #3 stated “I have a concern with the following references under Dermal Acute Exposure:

1. Union Carbide Corp. (1992b) was not listed in the text only in tables and I question whether this reference should remain in the citations if the study is not referenced in the text.
2. I understand that the study described Union Carbide Corp. (1992h) was a study in rabbits not rats. Similarly, this citation is listed under Ocular Acute Exposure.”

RESPONSE: *Union Carbide Corp. (1992b) is cited in numerous locations in the text. Entries for Union Carbide Corp. (1992h) in Appendix B Tables were checked; for those that were otherwise correct, the test animal was changed from rat to rabbit. References to Union Carbide Corp. (1992h) for rats in the ocular acute exposure section of Tables B-10 and B-16 were revised to Union Carbide Chem & Plas Co. (1991k) for rabbits.*

Reviewer #3 evaluation of unpublished studies cited in the ATSDR Toxicological Profile for Glutaraldehyde

Suggestions regarding deletion of selected unpublished studies from the toxicological profile with rationale for deletion.

COMMENT: BASF 1990k and Confidential 1974: Reviewer #3 stated “There are two citations that were impossible to decipher as to what was done, concentration used and whether there were more than one test group and thus they need to be deleted.” The reviewer indicated that BASF 1990k can be deleted because other acceptable studies cover the same topic. The reviewer noted that Confidential 1974 (a delayed hypersensitivity study in guinea pigs) was difficult to read and the experimental design difficult to follow, and that a number of other hypersensitivity studies in guinea pigs are reported.

RESPONSE: *BASF 1990k and Confidential 1974 were deleted.*

COMMENT: Union Carbide Chem & Plas Co. 1991bb: Reviewer #3 stated that this report “is not informative as similar studies on rabbits basically showed the same results. It is cited once in the profile on page 43 with other citations that are more relevant. No LD50 was determined and the study results were descriptive.”

RESPONSE: *Union Carbide Chem & Plas Co. (1991bb) was deleted.*

COMMENT: Union Carbide Corp. 1992k: Reviewer #3 stated “Only six female rats were tested and no control group was included. The concentration of glutaraldehyde in the exposure chamber is questionable. Two laboratories using different methods analyzed the samples and the difference in concentration was 10 fold; hence the study is not reliable. Therefore it should be removed from profile. No LT50 could be calculated. This study is only cited in the tables.”

RESPONSE: *This study was deleted from the profile.*

COMMENT: Union Carbide Chem & Plas Co. 1991b: Reviewer #3 stated “This citation provided a few LD50 values of different studies without any information as to what and how the studies were performed or even that glutaraldehyde was tested. It should be deleted from the profile.”

RESPONSE: *This report was deleted from the profile.*

COMMENT: Union Carbide Chem & Plas Co. 1991x: Reviewer #3 stated “This study reported on an inhalation study in rats using static and dynamic approaches. In the latter case, the concentration of glutaraldehyde changed over the four hours of exposure hence an accurate determination of the

concentration is questionable. I suggest this citation be removed from the profile. It is listed on pages 14, 44 and 89 within a list of other more reliable studies.”

RESPONSE: *This study was retained because the data are considered adequate for the intended purpose. Reviewer #2 considered it reliable.*

COMMENT: Union Carbide Corp. 1996: Reviewer #3 noted that Union Carbide Corp. 1976 and 1996 are the same reports and suggested deleting Union Carbide Corp. 1996 from the profile.

RESPONSE: *Union Carbide Corp. (1996) was deleted from the profile.*

Unpublished studies that Reviewer #3 indicated should be retained along with rationale for retention.

COMMENT: Union Carbide Chem & Plas Co. 1992: Reviewer #3 stated “The study was well performed and LD50 values were calculated for both males and females. This was the only study where an NMR analysis was presented and it was noted that the glutaraldehyde is made up of five main compounds which are believed to interact with one another in solution. Therefore this citation should remain in the profile.”

RESPONSE: *This study was retained.*

COMMENT: Union Carbide Corp. 1992a: Reviewer #3 indicated that the acute oral and dermal studies in rats should remain in the profile since LD50 values were determined.

RESPONSE: *This study was retained.*

COMMENT: Union Carbide Corp. 1992i: Reviewer #3 indicated that the acute gavage study of mice should remain in the profile because LD50 values were calculated.

RESPONSE: *This study was retained.*

COMMENT: Union Carbide Chem & Plas Co. 1991dd, 1991ee: Reviewer #3 indicated that these were the only canine studies mentioned in the profile, that they appear useful for establishing doses used in a longer-term drinking water study and, therefore, should remain in the profile.

RESPONSE: *These studies were retained.*

COMMENT: Union Carbide Corp. 1992a, 1992b, 1992c: Reviewer #3 stated that these “were the only studies where the dermal LD50’s were determined for rabbits. I believe these studies should remain in the profile.” The reviewer similarly indicated that Union Carbide Chem & Plas Co. 1991aa and 1991bb should remain in the profile.

RESPONSE: *These studies were retained.*

COMMENT: BASF 1990l, 1990m, 1991a, 1991b: Reviewer #3 stated “On reading through these reposts it appears that the BASF (1990l) report show the tables for the preliminary report that was followed up in BASF (1991b) and the BASF report (1990m) shows the tables of the preliminary study of BASF (1991a). The reports of BASF 1991 (a, b) describe the experimental design and the results obtained in the definitive report. Whether it is necessary to reference the BASF (1990 l and m) reports in the profile is up to the writers of the profile. The problem with the 1990) reports are that there is no description of the studies from which these data were obtained. It is just my educated guess that this is these data arose.”

RESPONSE: *These studies were retained.*

Reviewer #3 did not comment on other unpublished reports cited in the Toxicological Profile for Glutaraldehyde