FINAL
9-8-2009

Provisional Peer-Reviewed Toxicity Values for

2-Chloroacetaldehyde
(CASRN 107-20-0)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-CHLOROACETALDEHYDE (CASRN 107-20-0)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

2-Chloroacetaldehyde (CAA) is a metabolite of the human carcinogen vinyl chloride. The empirical formula for CAA is C_2H_3OCl, and Figure 1 shows the chemical structure.

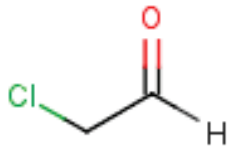

Figure 1. Chemical Structure Diagram for 2-Chloroacetaldehyde

The U.S. EPA has not derived RfDs, RfCs, or estimates of carcinogenic potency or risk for CAA. No values are posted on IRIS (U.S. EPA, 2008a), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997). Relevant documents in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) include a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1986) and a Health and Environmental Effects Document (HEED) (U.S. EPA, 1988). However, both of these documents conclude that no adequate data were available to derive quantitative estimates of noncarcinogenic or carcinogenic risk. The HEEP (U.S. EPA, 1986) and HEED (U.S. EPA, 1988) assign CAA to weight-of-evidence Group D for cancer.

U.S. EPA (2008b) lists interim Acute Exposure Guidelines (AEGLs) for CAA for use in the event of a sudden, unexpected release. The AEGL1 values (sensory irritation threshold) range from an 8-hour value of 0.22 ppm (0.7 mg/m^3) to a 10-minute value of 2.3 ppm (7.4 mg/m^3). The AEGL2 values (incapacitation) range from an 8-hour value of 0.39 ppm

(1.25 mg/m^3) to a 10-minute value of 9.8 ppm (31.5 mg/m^3). The AEGL3 values (death or serious, irreversible health effects) range from an 8-hour value of 1.8 ppm (5.8 mg/m^3) to a 10-minute value of 44 ppm (141 mg/m^3).

There are occupational exposure limits for 2-chloroacetaldehyde. The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) has adopted a Short-Term Exposure Limit (STEL) ceiling of 1 ppm (3 mg/m^3) for CAA. This value is intended to minimize the potential for ocular and upper respiratory tract irritation in exposed workers (ACGIH, 2007). The National Institute of Occupational Safety and Health (NIOSH, 2008) recommends a ceiling limit of 1 ppm (3 mg/m^3) for CAA based on the same effects. The Occupational Safety and Health Administration (OSHA, 2008) also lists a ceiling limit of 1 ppm (3 mg/m^3) for CAA.

The National Toxicology Program (NTP, 2008) has not assessed the toxicity or carcinogenicity of CAA, and this compound is not included in the 11th Report on Carcinogens (NTP, 2005). CAA has not been the subject of a monograph by the International Agency for Research on Cancer (IARC, 2008) or a toxicological profile by ATSDR (2008). CalEPA (2002, 2008a,b) has not derived exposure levels for chronic toxicity or carcinogenic potency for CAA.

To identify toxicological information pertinent to the derivation of provisional toxicity values for CAA, literature searches were conducted on October 29, 2008 using the following databases: MEDLINE, TOXLINE, BIOSIS (1999−October 2008), Chemical Abstracts (1999−October 2008), TSCATS1/2, CCRIS, DART, GENETOX, HSDB, RTECS, and Current Contents (April 2007−October 2008). An additional literature search was conducted on July 14, 2009 of MEDLINE. Except where noted, the literature searches were not limited by date.

REVIEW OF PERTINENT DATA

Human Studies

No relevant data were located regarding the toxicity of CAA to humans following inhalation or oral exposure.

Animal Studies

Oral Exposure

Designed primarily as a cancer bioassay of three different chlorinated water contaminants, Daniel et al. (1992) exposed 40 male B6C3F1 mice for 104 weeks to drinking water containing CAA at 0.1 g/L (equivalent to 17 mg/kg-day, as determined by study authors). Untreated control animals (23 in one group, from which interim euthanasias were conducted, and 10 in a second group) received distilled water. Interim sacrifices of five animals per group were conducted at 30 and 60 weeks of exposure. Complete necropsy and microscopic examination were performed. There were no statistically significant treatment-related effects on survival or body weight. There were no changes in spleen, kidneys, or testes weights, or histopathological changes in any tissue except the liver. Absolute and relative liver weights were slightly increased at the 30-week sacrifice but did not maintain statistical significance by 104 weeks

($p > 0.10$). At terminal sacrifice (104 weeks), hepatocellular necrosis was noted in 7/26 (27%) treated animals, compared to 1/20 (5%) in controls; mild cytoplasmic vacuolization, cytomegaly, and cytoplasmic alteration were also reported. Additionally, a significant increase in the incidence of liver tumors was found. The prevalence of liver neoplasms at terminal sacrifice was statistically significantly ($p \leq 0.03$) increased over controls, with carcinomas in 8/26 (31%) and adenomas in 2/26 (8%), as well as preneoplastic lesions (hyperplastic nodules) in 2/26 (8%). In control animals, carcinomas, adenomas, and nodules occurred in 2/20, 1/20, and 0/20, respectively. At the 60-week sacrifice, there were 1/5 treated animals with hepatocellular carcinoma, compared with 0/5 controls. No carcinomas, adenomas, or hyperplastic nodules were reported in animals sacrificed at Week 30.

Van Duuren et al. (1979) observed no significant increase in forestomach or internal tumors in Ha:ICR Swiss mice (30/sex) treated with 0.25 mg of CAA in water by intragastric intubation once per week for up to 636 days, compared with vehicle (30/sex) and untreated (60 males, 100 females) controls. Based on a reference body weight of 0.036 kg for mice in a chronic study (U.S. EPA, 1988), this corresponds to an average weekly dose of approximately 7 mg/kg in the treated mice.

Inhalation Exposure

No subchronic or chronic inhalation studies are available for derivation of an RfC or inhalation unit risk for CAA.

Other Studies

Other Routes

Lawrence et al. (1972) conducted studies of repeated intraperitoneal (i.p.) injection of CAA in rats. Male Sprague-Dawley rats were treated with CAA by i.p. injection at 0.001879 or 0.003758 mL/kg daily for 30 days or 0.00032, 0.0008, 0.0016, or 0.0032 mL/kg 3 times weekly for 12 weeks. Effects were seen primarily in the high-dose group in the 30-day study and the two highest dose groups in the 12-week study, and were similar in the two studies: reduced body weight gain; decreased red blood cell count, hemoglobin, and hematocrit; and histopathological lesions in the lungs (increased severity of bronchopneumonia and changes in respiratory epithelium relative to controls).

Van Duuren et al. (1979) reported negative results in cancer bioassays of CAA conducted in groups of 30 female Ha:ICR Swiss mice by dermal application (1 mg/mouse in 0.1-mL acetone, 3 times weekly, for 581 days) or subcutaneous injection (0.25 mg in water, once weekly, for 630 days) compared with vehicle (30/group) and untreated (100/group) controls. CAA also gave negative results as an initiator in a dermal initiation-promotion protocol with PMA (phorbol myristate acetate) as the promoter (Van Duuren et al., 1979).

Genotoxicity

CAA has been demonstrated to be mutagenic in a variety of in vitro assays using both prokaryotes and eukaryotes with and without metabolic activation (Bignami et al., 1980; Rannug et al., 1976; McCann et al., 1975; Malaveille et al., 1975; Phillips et al., 1980; Garro and Phillips, 1980; Hussain and Osterman-Golkar, 1984; Perrard, 1985; Lorprieno et al., 1977; Huberman et al., 1975; Rosenkranz, 1977; Jacobsen et al., 1989; Mroczkowska et al., 1993; Kohwi-Shigematsu and Nelson, 1988; Matsuda et al., 1995; Chiang et al., 1997; Tudek et al., 1999; Chang et al., 1992; Kandala et al., 1990). In human cell

lines, CAA was found to modify a specific site within the regulatory sequence of the human cytomegalovirus intermediate early (IE) gene (Kohwi-Shigematsu and Nelson, 1988), the *supF* gene of mutant plasmids transfected into human fibroblast cells (Matsuda et al., 1995), sites in the hypoxanthine (guanine) phosphoribosyl-transferase (hprt) locus of human B-lymphoblastoid cells (Chiang et al., 1997), and adenine, cytosine, and guanine bases in the human p53 tumor-suppressor gene contained in pSP65 plasmids grown in *Escherichia coli* strain DH5α (Tudek et al., 1999). The formation of CAA-induced DNA adducts, leading to the occurrence of mutations, has been confirmed (Jacobsen et al., 1989; Tudek et al., 1999). CAA induced promutagenic exocyclic etheno DNA adducts (e.g., 1,N^6-ethenodeoxyadenosine) in human B-lymphoid cells (Zielinski and Hergenhahn, 2001). CAA treatment caused dose-dependent increases in etheno DNA adducts (1,N^6-ethenodeoxyadenosine, 3,N^4-ethenodeoxycytidine, and 1,N^2-ethenodeoxyguanosine) and small increases in strand breaks and abasic sites in the *supF* gene of the pSP189 plasmid (Kim et al., 2007). The location of CAA−induced DNA adducts in *supF* target genes corresponds well with mutation data showing that mutations occur at many different base positions along the *supF* target (Choi and Pfeifer, 2004). The mutational spectra obtained with the *supF* target genes showed a preponderance of C/G to T/A transitions and C/G to A/T transversions (Choi and Pfeifer, 2004). In the human p53 gene, CAA-induced DNA damage was concentrated in sequences that showed secondary structure perturbations inhibiting DNA synthesis, which are mutation hot spots in the human p53 gene (Kowalczyk et al., 2006). Combined, these in vitro studies demonstrating possible mutagenicity for CAA do not correlate with the limited in vivo studies.

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL ORAL RfD VALUES FOR 2-CHLOROACETALDEHYDE

Because of the lack of human oral data and the inadequacy of the animal oral data, p-RfD values for CAA cannot be derived. The cancer bioassay study performed by Daniel et al. (1992) is limited in its application to noncancer risk assessment for two reasons: first, this study utilized only a single dose level; secondly, administration of CAA resulted in carcinogenic effects in the liver, which makes it difficult to distinguish between liver effects that may be precancerous and effects that may be distinct from the carcinogenic process.

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL INHALATION RfC VALUES FOR 2-CHLOROACETALDEHYDE

Provisional RfC values for CAA cannot be derived because of the lack of suitable human or animal inhalation data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-CHLOROACETALDEHYDE

Weight-of-Evidence Descriptor

No data were located regarding the carcinogenicity of CAA in humans. Daniel et al. (1992) found a significant increase in liver tumors in male mice treated with CAA for 2 years. However, only a single dose level was tested. Female mice were not assessed in this study. A series of studies performed by Van Duuren et al. (1979) in mice exposed by intragastric injection, subcutaneous injection, or dermal application were negative but were not adequate cancer bioassays. Genotoxicity data show that CAA is mutagenic in both bacteria and human cells. Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *"Suggestive Evidence of Carcinogenic Potential for 2-chloroacetaldehyde,"* based on a positive response in a limited animal bioassay and strong evidence of mutagenicity.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

Oral data are limited and include a single dose level study (Daniel et al., 1992) that can be used to derive a quantitative estimate of cancer risk for CAA. Because the cancer descriptor for this chemical is "*Suggestive Evidence of Carcinogenic Potential*," a screening p-OSF is provided in an appendix, which may be useful in certain instances. Please see the attached Appendix for details.

Inhalation Exposure

No inhalation studies are available to develop an inhalation unit risk estimate (IUR).

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. TLVs® and BEIs®: Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. ACGIH, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Online. www.atsdr.cdc.gov/toxpro2.html.

Bignami, M., G. Conti, L. Conti et al. 1980. Mutagenicity of halogenated aliphatic hydrocarbons in *Salmonella typhimurium*, *Streptomyces coelicolor* and *Aspergillus nidulans*. Chem. Biol. Interact. 30:9−23.

CalEPA (California Environmental Protection Agency). 2002. Hot Spots Unit Risk and Cancer Potency Values. Online. http://www.oehha.ca.gov/air/hot_spots/pdf/TSDlookup2002.pdf.

CalEPA (California Environmental Protection Agency). 2008a. OEHHA/ARB Approved Chronic Reference Exposure Levels and Target Organs. Online. http://www.arb.ca.gov/toxics/healthval/chronic.pdf.

CalEPA (California Environmental Protection Agency). 2008b. Air Chronic Reference Exposure Levels Adopted by OEHHA as of February 2005. Online. http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html.

Chang, L.W., F.B. Daniel and A.B. DeAngelo. 1992. Analysis of DNA strand breaks induced in rodent liver *in vivo*, hepatocytes in primary culture, and a human cell line by chlorinated acetic acids and chlorinated acetaldehydes. Environ. Mol. Mutagen. 20:277−288.

Chiang, S.Y., J.A. Swenberg, W.H. Weisman et al. 1997. Mutagenicity of vinyl chloride and its reactive metabolites, chloroethylene oxide and chloroacetaldehyde, in a metabolically competent human B-lymphoblastoid line. Carcinogenesis. 18:31−36.

Choi, J.-H. and G.P. Pfeifer. 2004. DNA damage and mutations produced by chloroacetaldehyde in a CpG-methylated target gene. Mutat. Res. 568:245−256.

Daniel, F.B., A.B. DeAngelo, J.A. Stober et al. 1992. Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde, and dichloroacetic acid in the male B6C3F1 mouse. Fundam. Appl. Toxicol. 19:159−168.

Garro, A.J. and R.A. Phillips. 1980. Detection of mutagen-induced lesions in isolated DNA by marker rescue of *Bacillus subtillis* phase 105. Mutat. Res. 73(1):1−13.

Huberman, E., H. Bartsch and L. Sachs. 1975. Mutation induction in Chinese hamster V79 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloroacetaldehyde. Int. J. Cancer. 16:639−644.

Hussain, S. and S. Osterman-Golkar. 1984. Dose-response relationships for mutations induced in *E. coli* by some model compounds. With an addendum: Reaction kinetics in water of chloroethylene oxide, chloroacetaldehyde, and chloroacetone. Hereditas. 101(1):57−68.

IARC (International Agency for Research on Cancer). 2008. Search IARC Monographs. Online. http://monographs.iarc.fr/ENG/Monographs/allmonos90.php.

Jacobsen, J.S., C.P. Perkins, J.T. Callahan et al. 1989. Mechanisms of mutagenesis by chloroacetaldehyde. Genetics. 121:213−222.

Kandala, J.C., J.E.K. Mrema, A. DeAngelo et al. 1990. 2-Chloroacetaldehyde and 2-chloroacetal are potent inhibitors of DNA synthesis in animal cells. Biochem. Biophys. Res. Comm. 167:457−463.

Kim, M.Y., X. Zhou, J.C. Delaney et al. 2007. AlkB influences the chloroacetaldehyde-induced mutation spectra and toxicity in the pSP189 *supF* shuttle vector. Chem. Res. Toxicol. 20:1075−1083.

Kohwi-Shigematsu, T. and J.A. Nelson. 1988. The chemical carcinogen, chloroacetaldehyde, modifies a specific site within the regulatory sequence of human cytomegalovirus major immediate early gene in vivo. Mol. Carcinogen. 1:20−25.

Kowalczyk, P., J.M. Ciesla, M. Saparbaev et al. 2006. Sequence-specific *p53* gene damage by chloroacetaldehyde and its repair kinetics in *Escherichia coli*. 53(2):337−347.

Lawrence, W.H., E.O. Dillingham, J.E. Turner et al. 1972. Toxicity Profile of Chloroacetaldehyde. J Pharm Sci. 61(1):19−25.

Lorprieno, N., R. Barale, S. Baroncelli et al. 1977. Induction of gene mutations and gene conversions by vinyl chloride metabolites in yeast. Canc. Res. 3(1):253−257.

Malaveille, C., H. Bartsch, A. Barbin et al. 1975. Mutagenicity of vinyl chloride, chloroethyleneoxide, chloroacetaldehyde, and chloroethanol. Biochem. Biophys. Res. Commun. 63:363−370.

Matsuda, T., T. Yagi, M. Kawanishi et al. 1995. Molecular analysis of mutations induced by 2-chloroacetaldehyde, the ultimate carcinogenic form of vinyl chloride, in human cells using shuttle vectors. Carcinogenesis. 16:2389−2394.

McCann, J., V. Simmon, D. Streitweiser et al. 1975. Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethan (ethylene dichloride), chloroethanol (ethylene chlorohydrin), vinyl chloride and cuclophosphamide. Proc. Natl. Acad. Sci. USA. 72(8):3190−3193.

Mroczkowska, M.M., I.K. Kolasa and J.T. Kusmierek. 1993. Chloroacetaldehyde-induced mutagenesis in *Escherichia coli*: Specificity of mutations and modulation by induction of the adaptive response to alkylating agents. Mutagenesis. 8:341−348.

NTP (National Toxicology Program). 2005. 11th Report on Carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Online. http://ntp-server.niehs.nih.gov/.

NTP (National Toxicology Program). 2008. Testing Status of Agents at NTP. Online. http://ntp.niehs.nih.gov:8080/index.html?col=010stat.

NIOSH (National Institute for Occupational Safety and Health). 2008. NIOSH Pocket Guide to Chemical Hazards. Index by CASRN. Online. http://www2.cdc.gov/nioshtic-2/nioshtic2.htm.

OSHA (Occupational Safety and Health Administration). 2008. OSHA Standard 1915.1000 for Air Contaminants. Part Z, Toxic and Hazardous Substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Perrard, M.H. 1985. Mutagenicity and toxicity of chloroethyleneoxide and chloroacetaldehyde. Experientia. 41:676−677.

Phillips, R.A., S.A. Zahler and A.J. Garro. 1980. Detection of mutagen-induced lesions in isolated DNA using a new *Bacillus subtilis* transformation-based assay. Mutat. Res. 74(4):267−281.

Rannug, U., R. Geothe and C.A. Wachmeister. 1976. The mutagenicity of chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride. Chem. Biol. Interact. 12:251−263.

Rosenkranz, H.S. 1977. Mutagenicity of halogenated alkanes and their derivatives. Environ. Health Perspect. 21:79−84.

Tudek, B., P. Kowalczyk and J.M. Ciesla. 1999. Localization of chloroacetaldehyde-induced DNA damage in human p53 gene by DNA polymerase fingerprint analysis. IARC Scientific Publications. 150:279−293.

U.S. EPA (U.S. Environmental Protection Agency). 1986. Health and Environmental Effects Profile (HEEP) for Chloroacetaldehyde. Environmental Criteria and Assessment Office. Office of Health and Environmental Assessment, Cincinnati, OH. June, 1989.

U.S. EPA (U.S. Environmental Protection Agency). 1988. Health and Environmental Effects Document (HEED) for Chloroacetaldehyde. Environmental Criteria and Assessment Office. Office of Health and Environmental Assessment, Cincinnati, OH. June, 1989.

U.S. EPA (U.S. Environmental Protection Agency). 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA (U.S. Environmental Protection Agency). 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA (U.S. Environmental Protection Agency). 1997. Health Effects Assessment Summary Tables (HEAST). FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB 97-921199.

U.S. EPA (U.S. Environmental Protection Agency). 2000. Benchmark Dose Technical Guidance Document. External Review Draft. EPA/630/R-00/001. October.

U.S. EPA (U.S. Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, National Center for Environmental Assessment, Washington, DC. EPA/630/P-03/001F. Online. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

U.S. EPA (U.S. Environmental Protection Agency). 2006. Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2006. Online. http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf.

U.S. EPA (U.S. Environmental Protection Agency). 2008a. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris/.

U.S. EPA (U.S. Environmental Protection Agency). 2008b. Acute Exposure Guideline Levels (AEGLs). Online. http://www.epa.gov/oppt/aegl/pubs/results44.htm.

Van Duuren, B.L., B.M. Goldschmidt, G. Loewengart, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Nat Cancer Inst. 63(6):1433−1439.

Zielinski, B. and M. Hergenhahn. 2001. 2-Chloroacetaldehyde induces εdA DNA adducts in DNA of Raji cells as demonstrated by an improved HPLC-fluoimetry method. Freseniun. J. Anal. Chem. 370:97−100.

APPENDIX A. DERIVATION OF A SCREENING ORAL SLOPE FACTOR FOR 2-CHLOROACETALDEHYDE (CASRN 107-20-0)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for 2-Chloroacetaldehyde (CAA). However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "Screening Value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

Oral data are limited but can be used to derive a quantitative estimate of cancer risk for CAA. Male mice exhibited increased incidences of hepatocellular tumors in a cancer bioassay that included a single dose level (Daniel et al., 1992). While it is undesirable to utilize a single-dose study for quantitative estimates of cancer risk, the U.S. EPA attempts to estimate the cancer oral slope factor (OSF) when at all possible and has used a linear extrapolation from a single dose in prior provisional cancer slope factor derivations. Additionally, while there is strong evidence of mutagenicity in a variety of in vitro tests, due to design deficiencies (i.e., single dose level) in the in vivo cancer bioassay, the mode of action of 2-chloroacetaldehyde cannot be clearly defined as mutagenic. Because the mode of action of CAA is not defined, the linear quantitative methodology was applied.

Table A-1 shows the dose-response data used in the quantitative cancer assessment. The dose in the Daniel et al. (1992) mouse study was first converted to a human equivalent dose (HED) by adjusting for differences in body weight between humans and mice. In accordance with U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, a factor of $BW^{3/4}$ was used for cross-species scaling. For doses expressed per unit body weight (mg/kg or mg/kg-day), the relationship is reciprocal, and the human dose (mg/kg) is obtained by multiplying the animal dose (mg/kg) by the ratio of animal:human body weight raised to the 1/4 power. Because the mice were exposed to drinking water containing 0.1 g/L CAA (equivalent to 17 mg/kg-day) for 104 weeks, no adjustment for discontinuous exposure or less-than-lifetime administration is necessary. The equation used to calculate the HED is shown below, and the HED is presented in Table A-1.

$$HED = Dose \times (W/70\ kg)^{1/4}$$

where

Dose = average daily animal dose (mg/kg-day)
W = average mouse body weight during the study (kg)
70 kg = reference human body weight (U.S. EPA, 1988)

Table A-1. Dose-Response Data for Liver Tumors in Male Mice Treated with 2-Chloroacetaldehyde in the Drinking Water for 104 Weeks[a]

Animal Dose (mg/kg-day)	Average Body Weight[b] (kg)	Human Equivalent Dose (HED) (mg/kg-day)	Incidence of Carcinomas			Incidence of Carcinomas and Adenomas (Combined)		
			60 wks	104 wks	60 + 104 wks	60 wks	104 wks	60 + 104 wks
0	NA	0	0/5	2/20	2/25	0/5	3/20	3/25
17	0.0241	2.32	1/5	8/26	9/31	1/5	10/26	11/31

[a]Daniel et al. (1992).
[b]Calculated from initial and final body-weight measurements made during the study.

Dose-response modeling of the data in Table A-1 was performed to obtain a point of departure (POD) for a quantitative assessment of cancer risk. The POD is an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range that marks the starting point for extrapolation to lower doses. There are several ways to analyze the data from Daniel et al. (1992); each possible approach was modeled and compared. Hepatocellular adenomas and carcinomas combined and carcinomas alone were modeled based on incidence at 104 weeks. Additionally, the combined incidence at the 60- and 104-week sacrifices for carcinomas alone and adenomas and carcinomas combined was modeled. Appendix A provides details of the modeling effort. Modeling results were similar for all four data sets. The $BMDL_{10HED}$ (lower bound on human equivalent dose estimated to produce a 10% increase in tumor incidence over background) was estimated using the U.S. EPA (2000) benchmark dose (BMD) methodology and benchmark response (BMR) of 10% extra risk. The lowest $BMDL_{10HED}$ was 0.37 mg/kg-day for combined hepatocellular adenomas and carcinomas in male mice sacrificed at 104 weeks.

The $BMDL_{10HED}$ of 0.37 mg/kg-day was selected as the POD for derivation of the p-OSF. In order to linearly extrapolate cancer risks from the $BMDL_{10HED}$ to the origin, the p-OSF was calculated as the ratio $BMR/BMDL_{10HED}$ (0.1 ÷ 0.37 mg/kg-day), as follows:

$$\begin{aligned} \textbf{p-OSF} &= BMR \div BMDL_{10HED} \\ &= 0.1 \div 0.37 \text{ mg/kg-day} \\ &= \mathbf{0.27 \text{ or } 2.7 \times 10^{-1} \text{ (mg/kg-day)}^{-1}} \end{aligned}$$

Given that the limited data available (only one treated dose level in the key study) constrained the model shape and precluded application of statistical methods to assess model fit, this p-OSF is highly uncertain.

The p-OSF for CAA should not be used with exposures exceeding the POD ($BMDL_{10HED}$ = 0.37 mg/kg-day) because the slope is not linear at higher doses. Above the POD, the fitted dose-response model better characterizes what is known about the carcinogenicity of CAA. Table A-2 shows the doses associated with specific levels of cancer risk based on the p-OSF estimated herein.

Table A-2. Doses of CAA Associated with Specific Levels of Cancer Risk	
Risk Level	**Dose (mg/kg-day)**
10^{-4}	0.0004
10^{-5}	0.00004
10^{-6}	0.000004

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR ORAL SLOPE FACTOR

Model Fitting Procedure for Cancer Incidence Data:

The model-fitting procedure for dichotomous cancer incidence data is as follows. The multistage-cancer model in the U.S. EPA benchmark dose modeling software (BMDS) is fit to the incidence data using the "extra risk" option. The multistage model is run for all polynomial degrees up to *n*-1 (where *n* is the number of dose groups including control); the degree polynomial with the lowest AIC is selected. Goodness-of-fit is assessed by the χ^2 test; adequate fit is indicated by a *p*-value greater than 0.1. In accordance with U.S. EPA (2000) *Benchmark Dose Technical Guidance Document*, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with a benchmark response (BMR) of 10% extra risk are calculated.

Model Fitting Results for Liver Tumors in Male Mice (Daniel et al., 1992):

Table B-1 shows the dose-response data on liver tumor incidence in male mice treated with 2-chloroacetaldehyde in drinking water for 104 weeks (Daniel et al., 1992). Hepatocellular adenomas and/or carcinomas were observed in the mice at both the 60-week interim sacrifice and terminal 104-week sacrifice. Therefore, modeling was performed for 4 separate data sets: (1) combined adenomas and carcinomas in male mice sacrificed at 104 weeks, (2) combined adenomas and carcinomas in male mice sacrificed at 60 or 104 weeks, (3) carcinomas alone in male mice sacrificed at 104 weeks, and (4) carcinomas alone in male mice sacrificed at 60 or 104 weeks.

Table B-1. Model Predictions for Liver Tumors in Male Mice[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	BMD_{10HED} (mg/kg-day)	$BMDL_{10HED}$ (mg/kg-day)
104 weeks only (degree = 1)[c]						
Carcinomas	0	0	NA	49.10	0.93	0.45
Carcinomas and Adenomas	0	0	NA	55.55	0.76	0.37
Pooled (60 + 104 weeks) (degree = 1)[c]						
Carcinomas	0	0	NA	55.29	0.94	0.49
Carcinomas and Adenomas	0	0	NA	61.23	0.79	0.42

[a]Daniel et al. (1992)

[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

[c]Only the 1-degree polynomial was run due to the use of only 2 dose groups in the study. Betas restricted to ≥ 0.

NA = Not Available

The incidence and human equivalent dose data were modeled according to the procedure outlined above using BMDS version 2.1 with default parameter restrictions. Due to the use of only a single treated group in the study, only the 1-degree model was run. With only a single

treated group and a background incidence above zero (i.e., a two-parameter model and two dose groups), there were insufficient degrees of freedom available to assess model fit for any of these data sets. Therefore, although BMD_{10} and $BMDL_{10}$ values were calculated, they should be considered to be highly uncertain.

Table B-1 and Figures B-1 through B-4 present the modeling results. Modeling results were similar for all four data sets. The lowest $BMDL_{10HED}$ was 0.37 mg/kg-day for combined hepatocellular adenomas and carcinomas in male mice sacrificed at 104 weeks.

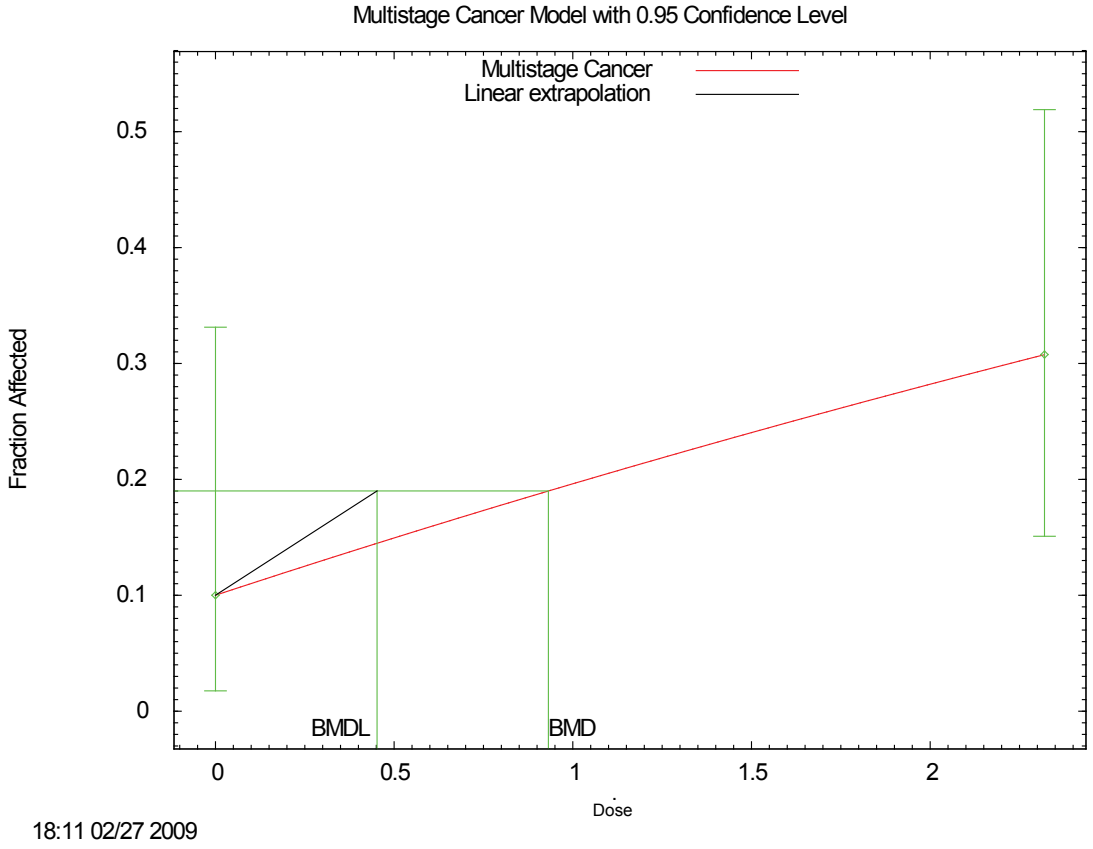

Figure B-1. Fit of Multistage (1-Degree) Model to Data on Hepatocellular Carcinomas in Male Mice at 104 Weeks (Daniel et al., 1992)

BMDs and BMDLs indicated are human equivalent doses associated with an extra risk of 10% and are in units of mg/kg-day.

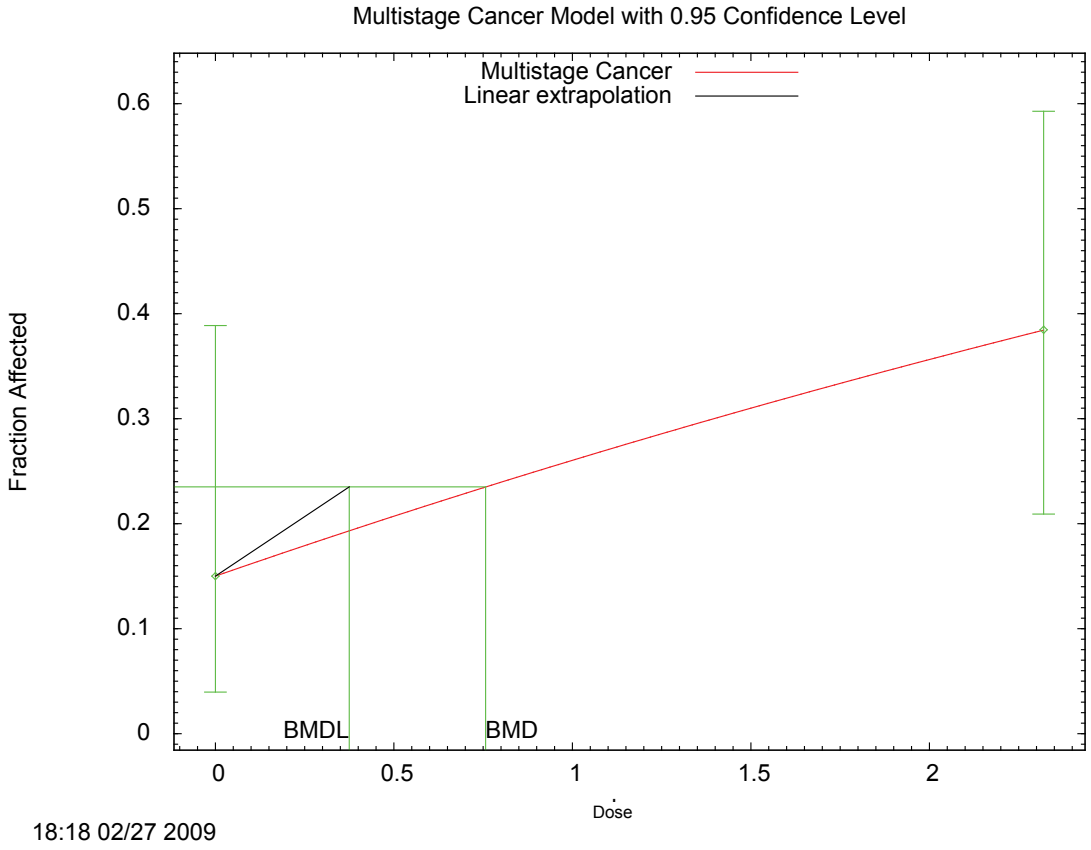

Figure B-2. Fit of Multistage (1-Degree) Model to Data on Hepatocellular Carcinomas or Adenomas (Combined) in Male Mice at 104 Weeks (Daniel et al., 1992)

BMDs and BMDLs indicated are human equivalent doses associated with an extra risk of 10% and are in units of mg/kg-day.

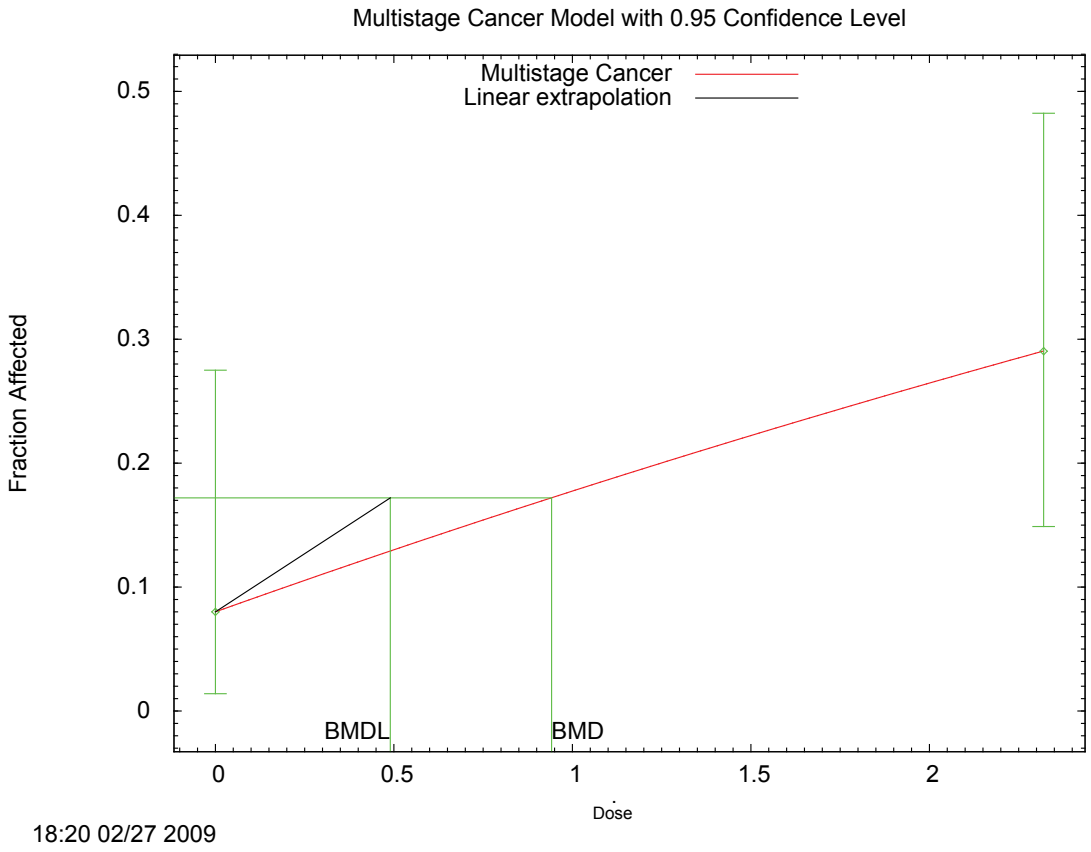

Figure B-3. Fit of Multistage (1-Degree) Model to Data on Hepatocellular Carcinomas in Male Mice at 60 and 104 Weeks (Daniel et al., 1992)

BMDs and BMDLs indicated are human equivalent doses associated with an extra risk of 10% and are in units of mg/kg-day.

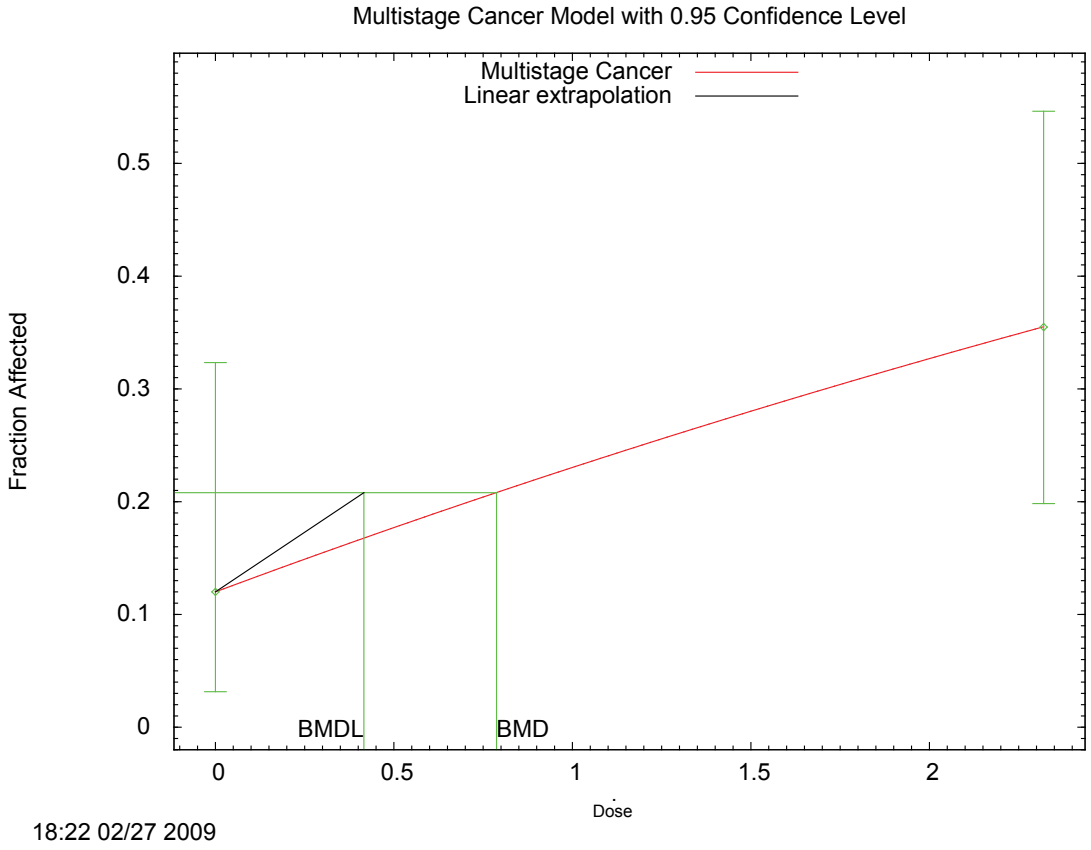

Figure B-4. Fit of Multistage (1-Degree) Model to Data on Hepatocellular Carcinomas or Adenomas (Combined) in Male Mice at 60 and 104 Weeks (Daniel et al., 1992)

BMDs and BMDLs indicated are human equivalent doses associated with an extra risk of 10% and are in units of mg/kg-day.