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Provisional Peer-Reviewed Toxicity Values for

1,1,2-Trichloroethane
(CASRN 79-00-5)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1,2-TRICHLOROETHANE (CASRN 79-00-5)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in 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 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 EPA IRIS Program. All provisional toxicity values receive internal review by two 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The IRIS database (U.S. EPA, 2010a) lists an RfD of 4×10^{-3} mg/kg-day for 1,1,2-trichloroethane (verified 1988) based on a NOAEL of 3.9 mg/kg-day for serum chemistry changes indicative of hepatotoxicity in female mice exposed to the chemical in the drinking water for 90 days (Sanders et al., 1985; White et al., 1985) and a composite uncertainty factor (UF_C) of 1000 (10 each for use of a subchronic-duration study, extrapolation from mice to humans, and protection of sensitive individuals). This RfD is also included on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006); the source is a Drinking Water Health Advisory document (U.S. EPA, 1989). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) also includes a Health Effects Assessment for 1,1,2-Trichloroethane (U.S. EPA, 1984) that does not, however, incorporate a noncancer toxicity assessment. The HEAST (U.S. EPA, 2010b) refers to IRIS for the RfD and lists a subchronic RfD of 4×10^{-2} mg/kg-day based on the same NOAEL—but with the UF_C reduced to 100 without the 10-fold factor for extrapolation to a chronic duration. ATSDR (1989) derived an intermediate oral minimal risk level (MRL) (analogous to a subchronic RfD) of 4×10^{-2} mg/kg-day by the same method. The World Health Organization (WHO, 2008) has not evaluated the toxicity of 1,1,2-trichloroethane.

An RfC for 1,1,2-trichloroethane is not available on the IRIS (U.S. EPA, 2010a) database or on the HEAST (U.S. EPA, 2010b). ATSDR (1989) declined to derive MRLs for inhalation exposure to 1,1,2-trichloroethane. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007), the National Institute for Occupational Safety and Health (NIOSH, 2008), and the Occupational Safety and Health Administration (OSHA, 2008) all list time-weighted average (TWA) occupational exposure levels of 10 ppm (55 mg/m^3) for 1,1,2-trichloroethane to protect against central nervous system depression, eye and upper respiratory tract irritation, and liver damage.

IRIS includes a cancer assessment for 1,1,2-trichloroethane (verified 7-23-86) in which the chemical was assigned to cancer weight-of-evidence (WOE) Group C (*Possible Human*

Carcinogen) and both an oral slope factor (OSF; 5.7×10^{-2} per mg/kg-day) and an inhalation unit risk (IUR; 1.6×10^{-5} per µg/m^3) were derived based on an increased incidence of hepatocellular carcinoma in B6C3F$_1$ mice administered the test material by gavage for 78 weeks (National Cancer Institute [NCI], 1978). The International Agency for Research on Cancer (IARC, 1991, 1999) classified 1,1,2-trichloroethane as Group 3 (*Unclassifiable*) with respect to carcinogenicity in humans based on no human data and limited evidence of carcinogenicity in animals (hepatocellular neoplasms and adrenal pheochromocytomas in male and female B6C3F$_1$ mice in the NCI, 1978 study). 1,1,2-Trichloroethane is not included in the National Toxicology Program (NTP, 2005) *11th Report on Carcinogens*.

Literature searches were conducted on sources published from 1960 through September 2010 for studies relevant to the derivation of provisional toxicity values for 1,1,2-trichloroethane. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (last 6 months). An Organisation for Economic Co-operation and Development Screening Information Data Set (OECD SIDS) submission on 1,1,2-trichloroethane from the Japanese Ministry of Foreign Affairs (1999) was also reviewed for relevant data.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

No relevant data were located regarding the toxicity of 1,1,2-trichloroethane to humans following oral or inhalation exposure.

ANIMAL STUDIES

Oral Exposure

Subchronic-duration Studies

Groups of male and female CD-1 mice (16/sex/group) were exposed to 1,1,2-trichloroethane in the drinking water for 90 days at concentrations of 20, 200, or 2000 mg/L, which the study authors equated to dosages of 0, 4.4, 46, and 305 mg/kg-day for males and 0, 3.9, 44, and 384 mg/kg-day for females (White et al., 1985; Sanders et al., 1985). Groups of 24 mice of each sex served as controls. Endpoints assessed included water consumption, body weight, selected organ weights, hematology, serum chemistry, hepatic microsomal activity, and humoral and cell-mediated immune status. Body-weight gain over the 90-day study was significantly reduced by 35% in high-dose males and corresponded with a significant 35−40% decrease in water consumption in this group. Terminal body weight was reduced 10% in the high-dose males compared with controls. There was no effect on body weight or water consumption in males of other dose groups or in females. Hematological findings, highlighted by slight (5−6%) statistically significant reductions in hemoglobin and hematocrit in high-dose females, were generally unremarkable. Serum enzyme changes of note included significant increases in cholesterol in high-dose males and females (30−35%), alkaline phosphatase (ALP) in high-dose males (60%) and females of all dose groups (20−40%, not increasing with dose), aspartate aminotransferase (AST or SGOT) in females of all dose groups (30−40%, not increasing with dose), and alanine aminotransferase (ALT or SGPT) in high-dose females (63%). Liver glutathione was significantly reduced by 16% in mid-dose males and 28% in high-dose males. In females, liver glutathione was not reduced and was actually significantly

increased in the high-dose group. Assays for microsomal enzyme activity showed no evidence of enzyme induction in males or females; there were significant decreases in cytochrome P-450 levels and aniline hydroxylase activity in mid- and high-dose females. Both absolute and relative liver weights were significantly increased by approximately 30% in high-dose females; other organ-weight changes in females were unremarkable. Organ-weight changes in males were secondary to the effect on body weight. Immunological evaluations revealed no effects on cell-mediated immunity (delayed-type hypersensitivity and popliteal lymph node proliferation responses to sheep red blood cells), but humoral immune status was depressed, as indicated by significant dose-related decreases in hemagglutination titers in mid- and high-dose males and females, and significantly decreased spleen lymphocyte responsiveness to the B-cell mitogen lipopolysaccharide in high-dose females. Macrophage function was significantly decreased in high-dose males, as indicated by the ability of peritoneal macrophages to phagocytize sheep red blood cells.

In this study (White et al., 1985; Sanders et al., 1985), the high-dose of 305−384 mg/kg-day produced reduced body-weight gain secondary to reduced water consumption in male mice, and mild toxicity to the liver in mice of both sexes, as indicated by increases in serum cholesterol in males and females, ALP in males, ALT in females, and liver weight in females (without evidence of hepatic microsomal enzyme induction). Smaller increases in ALP and AST in female mice of all dose groups did not increase with dose and are not considered to be related to treatment. Binding with glutathione is a detoxification pathway for 1,1,2-trichloroethane (ATSDR, 1989). As the dose of such a chemical increases, more glutathione is used to detoxify the chemical, and glutathione stored in the liver can become depleted. Toxic effects may become evident when the functional reserve capacity of the liver is exceeded. Depletion of liver glutathione, then, is not a toxic effect itself, but a biochemical change that can serve as a marker for toxicity. The data from male mice in this study suggest that toxic effects on the liver can occur with ≈30% depletion of liver glutathione (as in the high-dose group). The absence of evidence for any hepatotoxic effects in mid-dose male mice suggests that the 16% depletion of glutathione in this group is within the functional reserve capacity of the mouse liver for this chemical. Therefore, the 16% decrease in glutathione levels is not an adverse effect by itself, nor is it evidence that an adverse effect will be produced at this dose level. (It is not clear how to interpret the *increase* in glutathione levels in high-dose females.) Effects on microsomal enzyme activity reported in mid- and high-dose females are also considered to be biochemical changes that are not clearly adverse. Immunotoxicity assays found some results suggesting suppression of immune function by 1,1,2-trichloroethane in the mid- and high-dose groups, although not all of the tests produced consistent results. In conclusion, this study authors identified a NOAEL of 3.9 mg/kg-day and a LOAEL of 44 mg/kg-day based on hepatic and immunological effects. The study was limited by the relatively large number of sporadic and inconsistent findings and failure to evaluate histopathology.

Chronic-duration Studies

In a chronic-duration cancer bioassay by NCI (1978), rats and mice were administered 1,1,2-trichloroethane by gavage in corn oil for 78 weeks. Groups of Osborne-Mendel rats (50/sex/group) initially received doses of 30 or 70 mg/kg-day, 5 days/week. At Week 20, doses were increased to 50 and 100 mg/kg-day, respectively. Groups of $B6C3F_1$ mice (50/sex/group) were initially given 150 or 300 mg/kg-day, 5 days/week. At Week 20, the doses were increased

to 200 and 400 mg/kg-day, respectively. Untreated and vehicle controls (20/sex/species/group) were included. No treatment-related nonneoplastic lesions were reported in any groups of rats or mice. Both sexes of mice had dose-related increases in incidence of hepatocellular carcinoma; these results are the basis for the verified WOE classification and the OSF and the IUR that appear on the IRIS database (U.S. EPA, 2010a).

Reproductive/developmental Studies

In a developmental toxicity screen, groups of 30 pregnant female ICR/SIM mice were treated with 0 or 350 mg/kg-day of 1,1,2-trichloroethane by gavage in corn oil on Days 8−12 of gestation and allowed to litter (Seidenberg et al., 1986). A total of three dams died in the treated group versus none in the controls. It is not clear whether these deaths were due to chemical toxicity. Body-weight gain in the dams did not differ between the two groups. There were a total of 30 litters in the control group and 25 litters in the treated group, with no resorbed litters. There were no effects on pup survival or body weight, monitored up to Postnatal Day (PND) 3. This study found no evidence for developmental toxicity by 1,1,2-trichloroethane at 350 mg/kg-day.

Inhalation Exposure

Subchronic-duration Studies

Groups of 8-week-old Fischer 344 CDF (F344) Crl:BR rats (10/sex/group) were exposed by whole-body inhalation to 0 (filtered air), 15, 40, or 100 ppm of 1,1,2-trichloroethane (99.55% pure) vapor (measured concentrations) 6 hours/day, 5 days/week, for 13 weeks (minimum of 65 exposures) in an unpublished study (WIL Research Laboratories, 2002). Duration-adjusted concentrations in mg/m^3 were 0, 14.6, 39.0, and 97.5 mg/m^3 (e.g., 15 ppm × 5.46 mg/m^3 per ppm × 6/24 hours × 5/7 days = 14.6 mg/m^3). Rats were observed daily; detailed clinical examinations and body-weight and food consumption measurements were performed weekly. Ophthalmic examinations were made before exposure and near study termination. Hematology and serum chemistry variables were assessed prior to study termination. Comprehensive necropsies were conducted for all animals. Organ weights were evaluated for adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus, and thyroids/parathyroids. Comprehensive microscopic evaluations were made for all control and high-dose rats, as well as for larynx, kidneys, liver, lungs, nasal tissues, trachea, and gross lesions from all animals in the 15- and 40-ppm test groups. In the only notable deviation from the test protocol, on Day 56 of the study, control rats were inadvertently exposed to 15 ppm, and the 15-ppm group rats were inadvertently placed in the control chamber for the 6-hour exposure period.

There was no dose-related effect on mortality, and no clinical signs related to treatment were observed (WIL Research Laboratories, 2002). A female rat in the 15-ppm group was sacrificed in extremis on Day 30 of the study with red discharge around the eyes, decreased defecation, and impaired use of hind limbs; however, the study authors did consider these effects to be related to treatment because they occurred in a low-dose rat, and no similar observations were made in any of the rats exposed to higher concentrations. No other mortality or sacrifices in extremis occurred. Other than a small, transitory decrease in body weight (−6%) and food consumption in high-dose females at the end of the first week of the study, the data showed no time- or dose-related adverse effects on body weight or food consumption. Ophthalmology was unaffected. The data showed no treatment-related effects on hematological variables. The only statistically significant effects on serum chemistry were slight increases in mean cholesterol in

mid- and high-dose females (+15−16%) and high-dose males (+19%) and a slight decrease in mean glucose in high-dose females (−14%). The data showed no treatment-related findings with regard to organ weights. Gross necropsy results were unremarkable. Histopathological evaluations showed hepatocellular vacuolation in 3/10 females each in the 15- and 40-ppm treatment groups and in 5/10 males and 10/10 females in the 100-ppm treatment groups. The control incidences (and low- and mid-dose male incidences) were not reported but presumably were 0/10. Vacuolation was characterized by focal-to-multifocal distribution of small vacuoles in the cytoplasm of hepatocytes. No special staining techniques were used to identify the material in the vacuoles, but the researchers considered the morphology of the vacuoles to be consistent with lipid accumulation. The severity of vacuolation was graded as minimal in all dose groups, with no change in severity with dose. There were no other microscopic findings in hepatocytes. Lesions of the olfactory epithelium, including vacuolation/microcyst formation, atrophy, and respiratory epithelial metaplasia, were found predominantly in the 40- and 100-ppm treatment groups. More detailed discussions of these lesions and associated incidence data are presented in Table 1. There were no other treatment-related histopathological findings in exposed rats.

Hepatocellular vacuolation and increased serum cholesterol were both observed in mid-dose females and high-dose males and females. Both observations are consistent with changes in lipid handling in the liver. However, vacuolation was of minimal severity in all groups, and cholesterol increases were likewise small in all groups. There were no indications of more clearly adverse changes in the liver by gross or histopathological examination, organ-weight measurement, or serum chemistry (e.g., ALP, ALT, AST) at any exposure level tested. Given the minimal nature of the observed liver changes and lack of progression to more clearly adverse effects with increasing exposure level, the observed liver changes are not considered to be toxicologically significant. The study authors reached the same conclusion. In contrast, the nasal lesions represent a spectrum of effects ranging from vacuolation/microcyst formation at all exposure levels to more clearly adverse effects such as atrophy at 40 ppm and metaplasia at 100 ppm. The researchers considered vacuolation/microcyst formation in the olfactory epithelium to be "probably degenerative in nature." Because the incidence of vacuolation/microcysts in the 15-ppm group was low and the more clearly adverse lesions were found only at 40 ppm and above, the study authors characterized the low-exposure concentration of 15 ppm as a NOAEL. A LOAEL of 40 ppm ($LOAEL_{ADJ}$ = 39.0 mg/m^3) and a NOAEL of 15 ppm ($NOAEL_{ADJ}$ = 14.6 mg/m^3) are identified for this study based on nasal lesions in the olfactory epithelium of exposed rats.

In an unpublished study by Dow Chemical Company (briefly summarized by ACGIH, 2001; ATSDR, 1989; U.S. EPA, 1984), unspecified numbers of male and female rats, guinea pigs, and rabbits were exposed to 1,1,2-trichloroethane vapors at a concentration of 15 ppm, 7 hours/day, 5 days/week, for 6 months. No treatment-related adverse effects were noted regarding growth, mortality, organ weight, hematology, or clinical chemistry. Nor were there indications of treatment-related histopathologic changes. Female rats exposed to a 1,1,2-trichloroethane vapor concentration of 30 ppm, 7 hours/day, for 16 days, had minor fatty changes and cloudy swelling in the liver, but male rats appeared unaffected. The secondary accounts of these unpublished studies do not provide sufficient detail to provide a basis for an RfC for 1,1,2-trichloroethane.

Table 1. Incidence of Lesions in the Olfactory Epithelium in Rats Exposed by Inhalation to 1,1,2-Trichloroethane[a]

	Concentration (ppm)			
Endpoint/Sex	**0**	**15**	**40**	**100**
Male				
Vacuolation/microcysts[b]	1/10	2/10[c]	6/10[c]	10/10[c,d]
Atrophy[e]	0/10	0/10	6/10[c,d]	7/10[c,d]
Metaplasia[f]	0/10	1/10[g]	1/10[c]	3/10[c]
Female				
Vacuolation/microcysts[b]	1/10	4/10[c]	4/10[c]	8/10[c,d]
Atrophy[e]	0/10	0/10	7/10[c,d]	10/10[c,d]
Metaplasia[f]	0/10	0/10	1/10[c]	5/10[c,d]

[a]WIL Research Laboratories, 2002; incidence represents number of individuals affected/number examined; six sections (levels) were examined for each animal; no further details for the section levels were described in the report.
[b]Small focal-to-multifocal vacuoles or microcysts primarily concentrated in the epithelium of the nasal septum in the dorsal medial meatus (Section Levels 2−5, except in low-concentration groups). Vacuoles were generally devoid of material with occasional eosinophilic globular material.
[c]Highlighted by study authors as "test article-related" based on details of examined sections (six/rat) and dose response.
[d]Statistically significant difference from control ($p < 0.05$) by Fisher's Exact test performed for this review.
[e]Thinning of olfactory epithelium due primarily to reduced thickness of nuclear cell layer; minimal-to-mild severity in Section Levels 3, 4, and 5; focal in distribution; affecting primarily the epithelium of the nasal septum in the dorsal medial meatus. The mechanism of cell loss was not obvious.
[f]Focal areas of metaplastic change from olfactory to respiratory epithelium; Section Levels 4 and 5.
[g]Not considered by study authors to be related to exposure; associated with inflammation within the nasal cavity and, therefore, interpreted to be spontaneous in origin.

A single male dog and 24 Sprague-Dawley rats (12/sex) were exposed to 1,1,2-trichloroethane at a target vapor concentration of 100 ppm (mean measured concentration of 84 ppm), 7 hours/day (on alternate days), for up to 6 months (Mellon Institute, 1947). Air-exposed animals (1 dog and 12 rats/sex) served as controls. Endemic lung infection in the entire rat colony resulted in high mortality among treated and control rats (57 and 62%, respectively) during the study and rendered it unusable for determining the toxicity of 1,1,2-trichloroethane. The treated dog exhibited a 13.2% decrease in body-weight gain relative to the control dog, but no obvious treatment-related effects on hematology or clinical chemistry, and no pathological signs. Inclusion of only a single treated dog is an obvious limitation of this study.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,1,2-TRICHLOROETHANE

SUBCHRONIC p-RfD

The subchronic-duration mouse study (White et al., 1985; Sanders et al., 1985) identified the liver and immune systems as sensitive targets of 1,1,2-trichloroethane toxicity. A NOAEL of 3.9 mg/kg-day and a LOAEL of 44 mg/kg-day were defined by a WOE for hepatotoxicity (significant increases in serum cholesterol in high-dose males and females, ALP in high-dose males, ALT in high-dose females, and liver weight [without evidence of enzyme induction] in high-dose females) and depressed immune status (significant dose-related decreases in hemagglutination titers in mid- and high-dose males and females, spleen lymphocyte responsiveness to the B-cell mitogen lipopolysaccharide in high-dose females, and macrophage function in high-dose males). Because the toxic effects were identified as the WOE of a number of different specific endpoints and it is unclear to what extent the individual immunological assays can be considered reliable markers of immunotoxicity, benchmark dose (BMD) modeling of individual test results was not performed. There is support for the liver as a sensitive target for 1,1,2-trichloroethane from acute and injection studies (ATSDR, 1989). The chronic-duration NCI (1978) study observed hepatocellular carcinomas in mice, which also supports the liver as a target for 1,1,2-trichloroethane. This study did not report noncancer lesions in the liver, but the study was conducted primarily as a cancer bioassay, and the extent of the evaluation for noncancer lesions is unclear. The Seidenberg et al. (1986) study, although only a screen, suggests that the developing fetus is not a critical target for 1,1,2-trichloroethane toxicity.

A subchronic p-RfD is derived by applying a UF_C of 1000 to the NOAEL of 3.9 mg/kg-day as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{NOAEL} \div UF_C \\ &= 3.9 \text{ mg/kg-day} \div 1000 \\ &= \textbf{0.004 or } \mathbf{4 \times 10^{-3}} \textbf{ mg/kg-day} \end{aligned}$$

The UF_C of 1000 is composed of the following:

- A UF_A of 10 for interspecies extrapolation was applied to account for potential pharmacokinetic and pharmacodynamic differences between mice and humans.
- A UF_H of 10 for intraspecies differences was applied to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF_D of 10 was applied to account for deficiencies in the database. The database includes limited subchronic-duration, chronic-duration, and developmental toxicity studies. The database lacks complete systemic toxicity data (most notably, histopathology), a complete developmental toxicity study, and a multigeneration reproduction study.

Confidence in the critical study is low to medium. The study included an adequate number of mice of each sex and an adequate number of dose groups and identified both a NOAEL and a LOAEL. The study was limited by a relatively large number of sporadic and inconsistent findings, and failure to perform histopathological examination. Confidence in the

database is low due to the lack of reproductive testing, limited developmental toxicity testing, and absence of other adequate chronic- or subchronic-duration systemic toxicity studies. Overall confidence in the subchronic p-RfD is low.

CHRONIC p-RfD

A verified (1988) RfD of 4×10^{-3} mg/kg-day for 1,1,2-trichloroethane is posted on the IRIS database (U.S. EPA, 2010a). The RfD is based on a LOAEL of 44 mg/kg-day and a NOAEL of 3.9 mg/kg-day in mice in the 90-day drinking water study (Sanders et al., 1985; White et al., 1985) and a UF_C of 1000 (10 each for use of a subchronic-duration study, extrapolation from mice to humans, and protection of sensitive individuals). A UF_D was not included, as this RfD was derived before application of a UF_D became standard practice.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,1,2-TRICHLOROETHANE

No subchronic or chronic p-RfC can be derived for the following reason: the only suitable study for deriving RfC values is a nonpeer-reviewed rat study by WIL Research Laboratories (2002). A screening subchronic and chronic p-RfC are developed in Appendix A. Please see the attached Appendix A for details.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,1,2-TRICHLOROETHANE

IRIS (U.S. EPA, 2010a) posts a cancer assessment for 1,1,2-trichloroethane (verified 7-23-86) that assigns a cancer WOE Group C (*Possible Human Carcinogen*); this classification is based on statistically significant increases in hepatocellular carcinoma in $B6C3F_1$ mice and pheochromocytomas in female $B6C3F_1$ mice (NCI, 1978). IRIS posts an OSF (5.7×10^{-2} per mg/kg-day) and an IUR (1.6×10^{-5} per $\mu g/m^3$); both are based on an increased incidence of hepatocellular carcinoma in $B6C3F_1$ mice administered the test material by gavage for 78 weeks (NCI, 1978).

Recently, a PBPK model for 1,1,2-trichloroethane in rats and mice was developed (The Sapphire Group, 2003) based on previous work (Gargas and Andersen, 1989) and new experimental studies (Poet et al., 2003). The model was applied for route-to-route extrapolation of the NCI (1978) cancer data from oral-to-inhalation exposure (The Sapphire Group, 2004). The model predicted that the 195-mg/kg-day (5 days/week) cancer LOAEL in mice in the NCI (1978) study was equivalent to a continuous inhalation exposure concentration of 27 ppm in female mice.

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR 1,1,2-TRICHLOROETHANE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional subchronic or chronic p-RfC for 1,1,2-trichloroethane. 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.

The subchronic-duration inhalation study conducted with rats by WIL Research Laboratories (2002) is the only study suitable for use in the derivation of p-RfC values. Both systemic and respiratory effects were observed. Systemic effects included hepatocellular vacuolation and increased serum cholesterol in mid-dose females and high-dose males and females, suggesting a possible treatment-related effect on lipid metabolism. However, these changes were minimal in all affected groups, and there were no more clearly adverse liver effects at any exposure level. This differs from the oral data, where increases in serum cholesterol were larger and accompanied by increases in liver weight and serum enzymes indicative of liver damage (ALP, ALT). The liver changes observed following inhalation exposure were not considered to be toxicologically significant. The observed respiratory effects comprised lesions of the olfactory epithelium of the nasal turbinates, ranging from vacuolation/microcyst formation (characterized by the researchers as "probably degenerative in nature") to atrophy and respiratory epithelial metaplasia. A low incidence of vacuolation/microcyst formation was the only effect at 15 ppm; more clearly adverse lesions (atrophy, metaplasia) and higher incidences of vacuolation/microcysts were seen at ≥40 ppm. A LOAEL of 40 ppm ($LOAEL_{ADJ}$ = 39.0 mg/m^3) and a NOAEL of 15 ppm ($NOAEL_{ADJ}$ = 14.6 mg/m^3) were identified for this study on this basis.

The data sets for nasal lesions (vacuolation/microcysts, atrophy, metaplasia) from WIL Research Laboratories (2002) were all subjected to BMD modeling to determine a point of departure (POD) for the derivation of p-RfC values. Vacuolation/microcyst formation was included as a sensitive indicator of nasal effects. Although not necessarily adverse by itself, it was considered to be "probably degenerative" by the study authors and occurred in the key study as part of a spectrum of lesions of the olfactory epithelium including more clearly adverse effects. Benchmark dose modeling software (BMDS; version 2.0) was used to run models for each of the data sets shown in Table 1. A benchmark response of 10% was used, as recommended by EPA (2000) for quantal data. Details of the model-fitting procedure and output are presented in Appendix B. All data sets were successfully modeled. BMD and benchmark dose lower bound 95% confidence interval (BMDL) values from the best fitting model for each data set are shown in Table A.1. The lowest BMDL values were obtained for vacuolation/microcyst formation in males and females and atrophy in males, all of which were within approximately 1 mg/m^3 of each other (3.9−5.0 mg/m^3).

Table A.1. BMD Modeling Results from Best Fitting Models for Lesions in the Nasal Olfactory Epithelium of Rats[a]		
Endpoint	**BMD_{10ADJ} (mg/m^3)**	**$BMDL_{10ADJ}$ (mg/m^3)**
Vacuolation/microcysts in males	13.7	3.9
Vacuolation/microcysts in females	7.4	4.4
Atrophy in males	7.9	5.0
Atrophy in females	32.9	14.3
Metaplasia in males	25.7	11.8
Metaplasia in females	38.7	16.1

[a]WIL Research Laboratories, 2002; values are duration-adjusted concentrations.

Based on the values shown in Table A.1, the $BMDL_{10ADJ}$ of 3.9 mg/m^3 for vacuolation/microcysts in male rats is the lowest value, and as such, is used for the POD in deriving screening subchronic and chronic p-RfC values for 1,1,2-trichloroethane. Given that 1,1,2-trichloroethane induced portal-of-entry nasal lesions, the following dosimetric adjustments were made to convert the $BMDL_{10ADJ}$ value for rodents to a human equivalent concentration (HEC) (U.S. EPA, 1994b). A Regional Gas Deposition Ratio (RGDR) of 0.13 was calculated as follows (Equation 4-18 and default variables from U.S. EPA, 1994b):

$$RGDR_{ET} = \frac{(V_E/SA_{ET})_{rat}}{(V_E/SA_{ET})_{human}} = 0.13$$

Where:

V_E = Minute volume (L/min)
= 0.137 L/min for male F344 rats (based on default body wt of 180 mg in a subchronic-duration study) and 13.8 L/min for humans

SA_{ET} = Surface area of the extrathoracic region (cm^2)
= 15 cm^2 for rats, 200 cm^2 for humans

The $BMDL_{HEC}$ of 0.51 mg/m^3 was subsequently derived as

$$BMDL_{10HEC} = RGDR_{ET} \times BMDL_{10ADJ}$$
$$= 0.13 \times 3.9$$
$$= 0.51\ mg/m^3$$

SCREENING SUBCHRONIC p-RfC

To derive the screening subchronic p-RfC for 1,1,2-trichloroethane, a UF_C of 300 was applied to the $BMDL_{10HEC}$, as follows:

$$\textbf{Screening subchronic p-RfC} = BMDL_{10HEC} \div UF_C$$
$$= 0.51\ mg/m^3 \div 300$$
$$= \mathbf{2 \times 10^{-3}\ mg/m^3}$$

The UF_C of 300 is composed of the following:

- A UF_A of 3 ($10^{0.5}$) was applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- A UF_H of 10 for intraspecies differences was applied to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF_D of 10 for database uncertainty was applied. The database for 1,1,2-trichloroethane contains only one adequate subchronic-duration inhalation study. There are no supporting systemic toxicity studies or developmental or reproductive toxicity studies.

Confidence in the critical study is medium. The study included an adequate number of rats of each sex and an adequate number of dose groups, examined comprehensive endpoints, identified both a NOAEL and a LOAEL, and was well reported (sufficient to support BMD modeling). The study has not been peer reviewed, however. Confidence in the database is low due to the lack of reproductive and developmental toxicity testing and the absence of supporting subchronic- or chronic-duration systemic toxicity studies. Overall confidence in the screening subchronic p-RfC is low.

SCREENING CHRONIC p-RfC

To derive the screening chronic p-RfC for 1,1,2-trichloroethane, a UF_C of 3000 was applied to the $BMDL_{10HEC}$, as follows:

$$\textbf{Screening chronic p-RfC} = BMDL_{10HEC} \div UF_C$$
$$= 0.51\ mg/m^3 \div 3000$$
$$= \mathbf{2 \times 10^{-4}\ mg/m^3}$$

The UF_C of 3000 is composed of the following:

- A UF_A of 3 ($10^{0.5}$) was applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- A UF_H of 10 for intraspecies differences was applied to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF_S of 10 was applied for using a subchronic-duration study to approximate chronic-duration exposure.
- A UF_D of 10 for database uncertainty was applied. The database for 1,1,2-trichloroethane contains only one adequate subchronic-duration inhalation study. There are no chronic-duration, developmental, or reproductive toxicity studies.

As discussed for the screening subchronic p-RfC, confidence in the principal study is medium, and confidence in the database and screening chronic p-RfC are low.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR SCREENING SUBCHRONIC p-RfC

MODEL-FITTING PROCEDURE FOR DICHOTOMOUS DATA

The model-fitting procedure for dichotomous data is as follows. All available dichotomous models in the EPA benchmark dose modeling software are 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 lowest degree polynomial providing adequate fit is used for comparison with the other models, per EPA (2000) guidance. Goodness-of-fit is assessed by the χ^2 test. Models with a χ^2 goodness-of-fit p-value ≥ 0.1 are considered to have adequate fit. Scaled residuals near the benchmark response, as well as visual inspection of the graphs associated with each model run, are also considered in evaluating the adequacy of fit. When several models provide adequate fit to the data (χ^2 $p \geq 0.1$, scaled residuals ≤ 2.0, visual inspection validates adequacy of fit), models are compared using the Akaike Information Criterion (AIC). The model with the lowest AIC is considered to provide the best fit to the data. When several models have the same AIC, the model resulting in the lowest benchmark dose lower bound 95% confidence interval (BMDL) is selected. In accordance with EPA (2000) guidance, benchmark doses (BMDs) and BMDLs associated with an extra risk of 10% are calculated for all models.

MODEL-FITTING RESULTS FOR INCIDENCE OF METAPLASIA OF OLFACTORY RESPIRATORY EPITHELIUM IN MALE RATS (WIL Research Laboratories, 2002)

All models provide adequate fit (see Table B-1). The log-logistic model has the lowest AIC value, and is, therefore, chosen as the best fitting model for this data set (see Figure B-1).

Table B-1. Model Predictions for Incidence of Metaplasia of Olfactory Epithelium in Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit p-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	3	0.54	0.9093	27.6909	27.9939	14.4868
Logistic	2	0.79	0.6735	30.3402	54.7621	34.9704
Log-logistic (slope ≥ 1)	**3**	**0.46**	**0.9286**	**27.6441**	**25.7126**	**11.7901**
Log-probit (slope ≥ 1)	2	1.03	0.5970	30.5384	48.7572	24.3648
Multistage (degree = 1, betas ≥ 0)	3	0.54	0.9093	27.6909	27.9939	14.4868
Multistage (degree = 2, betas ≥ 0)	3	0.54	0.9093	27.6909	27.9939	14.4868
Multistage (degree = 3, betas ≥ 0)	3	0.54	0.9093	27.6909	27.9939	14.4868
Probit	2	0.78	0.6767	30.2872	51.3098	32.3413
Weibull (power ≥ 1)	3	0.54	0.9093	27.6909	27.9939	14.4868
Quantal Linear	3	0.54	0.9093	27.6909	27.9939	14.4868

[a]WIL Research Laboratories, 2002

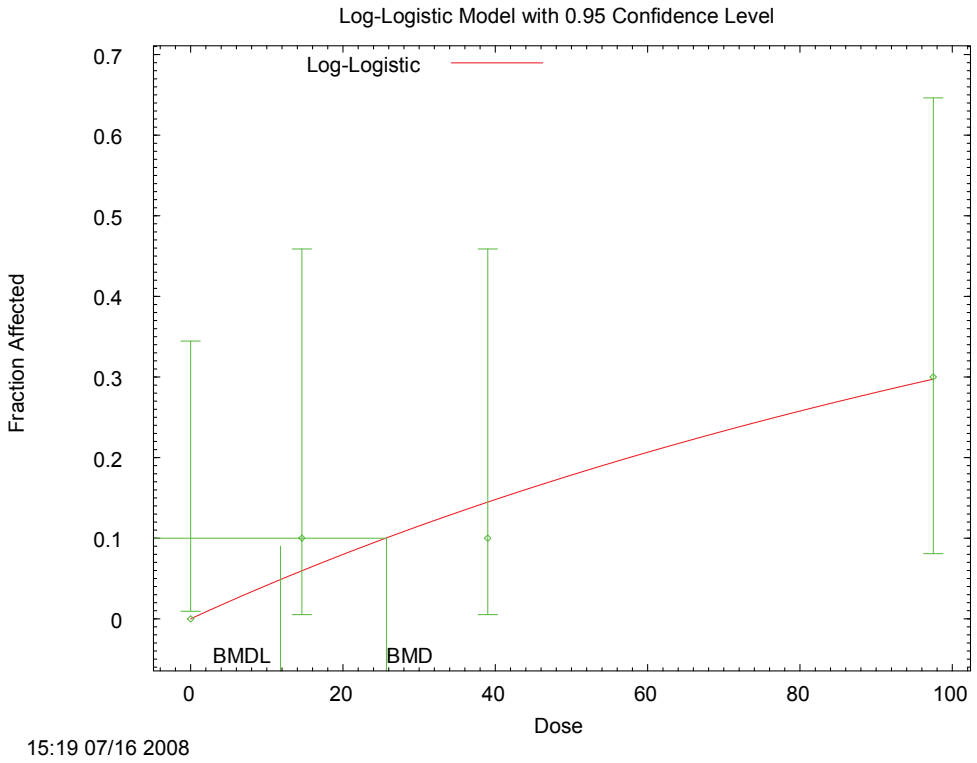

Figure B-1. Best Fitting Model for Nasal Metaplasia in Male Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.

MODEL-FITTING RESULTS FOR INCIDENCE OF METAPLASIA OF OLFACTORY EPITHELIUM IN FEMALE RATS (WIL Research Laboratories, 2002)

All models provide adequate fit to the data (see Table B-2). On the basis of the lowest AIC, the 2-degree multistage model (see Figure B-2) has the best fit.

Table B-2. Model Predictions for Incidence of Metaplasia of Olfactory Respiratory Epithelium in Female Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness- of-Fit *p*-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	2	0.09	0.9559	24.5114	41.7446	16.8434
Logistic	2	0.61	0.7379	25.1976	52.9053	33.7445
Log-logistic (slope ≥ 1)	2	0.10	0.9509	24.5346	41.6801	17.2468
Log-probit (slope ≥ 1)	2	0.04	0.9812	24.4297	40.03	21.3577
Multistage (degree = 1, betas ≥ 0)	3	1.74	0.6284	24.8265	21.5612	11.7056
Multistage (degree = 2, betas ≥ 0)	**3**	**0.16**	**0.9842**	**22.6709**	**38.6873**	**16.1186**
Multistage (degree = 3, betas ≥ 0)	2	2	0.9302	24.614	42.5194	16.2985
Probit	2	0.44	0.8036	24.9647	49.168	31.234
Weibull (power ≥ 1)	2	0.13	0.9345	24.5847	42.6364	16.4894
Quantal Linear	3	1.74	0.6284	24.8265	21.5611	11.7056

[a]WIL Research Laboratories, 2002

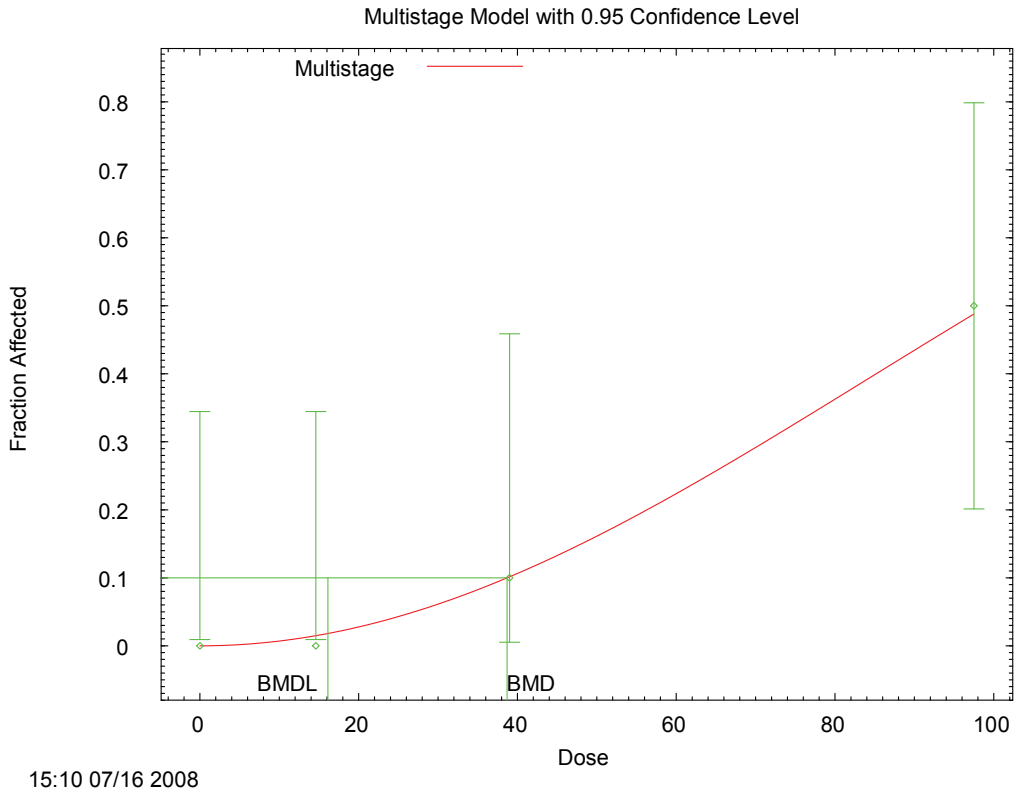

Figure B-2. Best Fitting Model for Nasal Metaplasia in Female Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.

MODEL-FITTING RESULTS FOR INCIDENCE OF VACUOLATION/MICROCYSTS IN NASAL OLFACTORY EPITHELIUM IN MALE RATS (WIL Research Laboratories, 2002)

All models provide adequate fit (see Table B-3). The 2-degree multistage model (see Figure B-3) yields the lowest AIC value and, therefore, is chosen as the best fitting model for this data set.

Table B-3. Model Predictions for Incidence of Vacuolation/Microcysts in Nasal Olfactory Epithelium in Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	1	0.19	0.6618	36.2229	17.3851	4.2487
Logistic	2	0.14	0.9323	34.1886	11.5423	7.21718
Log-logistic (slope ≥ 1)	2	0.39	0.8219	34.3686	34.2933	7.13212
Log-probit (slope ≥ 1)	1	0.39	0.5312	36.3686	31.1043	7.14513
Multistage (degree = 1, betas ≥ 0)	2	2.14	0.3431	37.0322	4.2804	2.69705
Multistage (degree = 2, betas ≥ 0)	**2**	**0.06**	**0.9727**	**34.0681**	**13.6836**	**3.92139**
Multistage (degree = 3, betas ≥ 0)	1	0.00	0.9803	35.9711	13.6079	3.69657
Probit	2	0.10	0.9523	34.0951	10.6275	6.87619
Weibull (power ≥ 1)	1	0.04	0.8429	36.0214	15.6032	4.43506
Quantal Linear	2	2.14	0.3430	37.0322	4.28032	2.69705

[a]WIL Research Laboratories, 2002

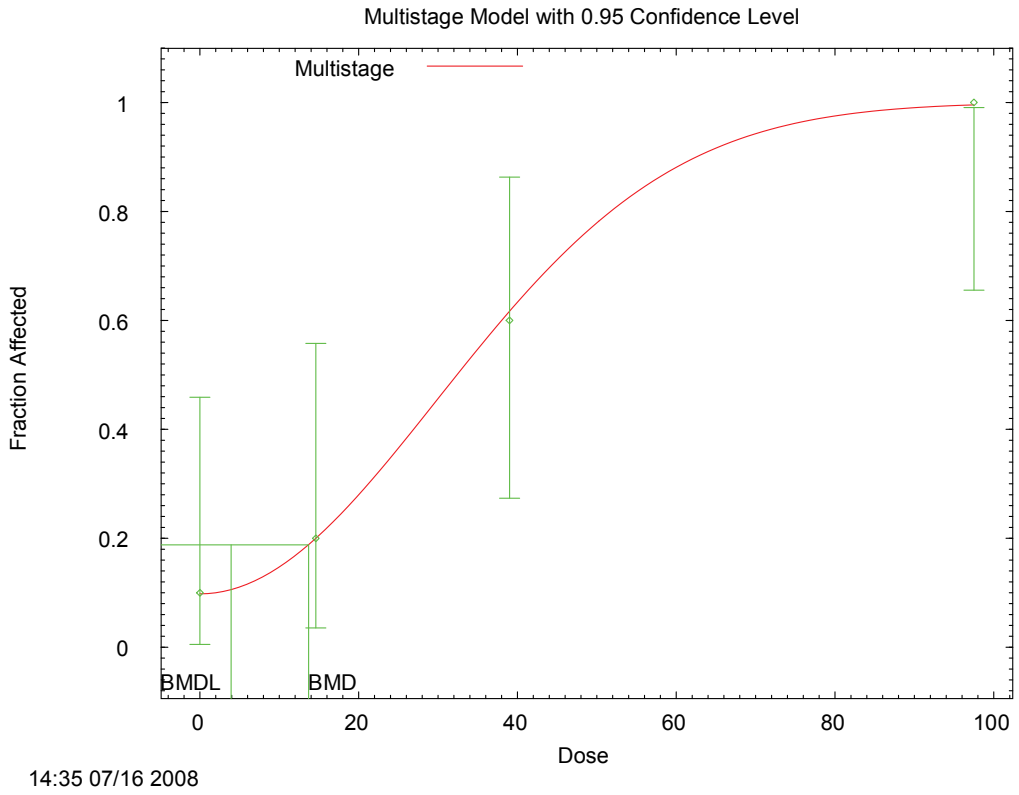

Figure B-3. Best Fitting Model for Vacuolation/Microcysts in Nasal Olfactory Epithelium in Male Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.

MODEL-FITTING RESULTS FOR INCIDENCE OF VACUOLATION/MICROCYSTS IN NASAL OLFACTORY EPITHELIUM IN FEMALE RATS (WIL Research Laboratories, 2002)

All models provide adequate fit (see Table B-4). The gamma, 1-degree multistage, 2-degree multistage, Weibull, and quantal linear models provide identical fit and the lowest AIC; the BMDL value from these models is chosen to represent the data set. The gamma model is representative of these models (see Figure B-4).

Table B-4. Model Predictions for Incidence of Vacuolation/Microcysts in Nasal Olfactory Epithelium in Female Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	**2**	**1.06**	**0.5900**	**48.4574**	**7.38404**	**4.36516**
Logistic	2	1.47	0.4793	48.9266	15.4579	10.1475
Log-logistic (slope ≥ 1)	1	1.17	0.2788	50.6072	5.37071	2.20114
Log-probit (slope ≥ 1)	2	1.81	0.4038	49.1768	13.6485	7.50422
Multistage (degree = 1, betas ≥ 0)	**2**	**1.06**	**0.5900**	**48.4574**	**7.38404**	**4.36516**
Multistage (degree = 2, betas ≥ 0)	**2**	**1.06**	**0.5900**	**48.4574**	**7.38404**	**4.36516**
Multistage (degree = 3, betas ≥ 0)	1	1.04	0.3067	50.442	7.95963	4.37088
Probit	2	1.44	0.4871	48.8872	14.9474	10.2404
Weibull (power ≥ 1)	**2**	**1.06**	**0.5900**	**48.4574**	**7.38405**	**4.36516**
Quantal Linear	**2**	**1.06**	**0.5900**	**48.4574**	**7.38404**	**4.36516**

[a]WIL Research Laboratories, 2002

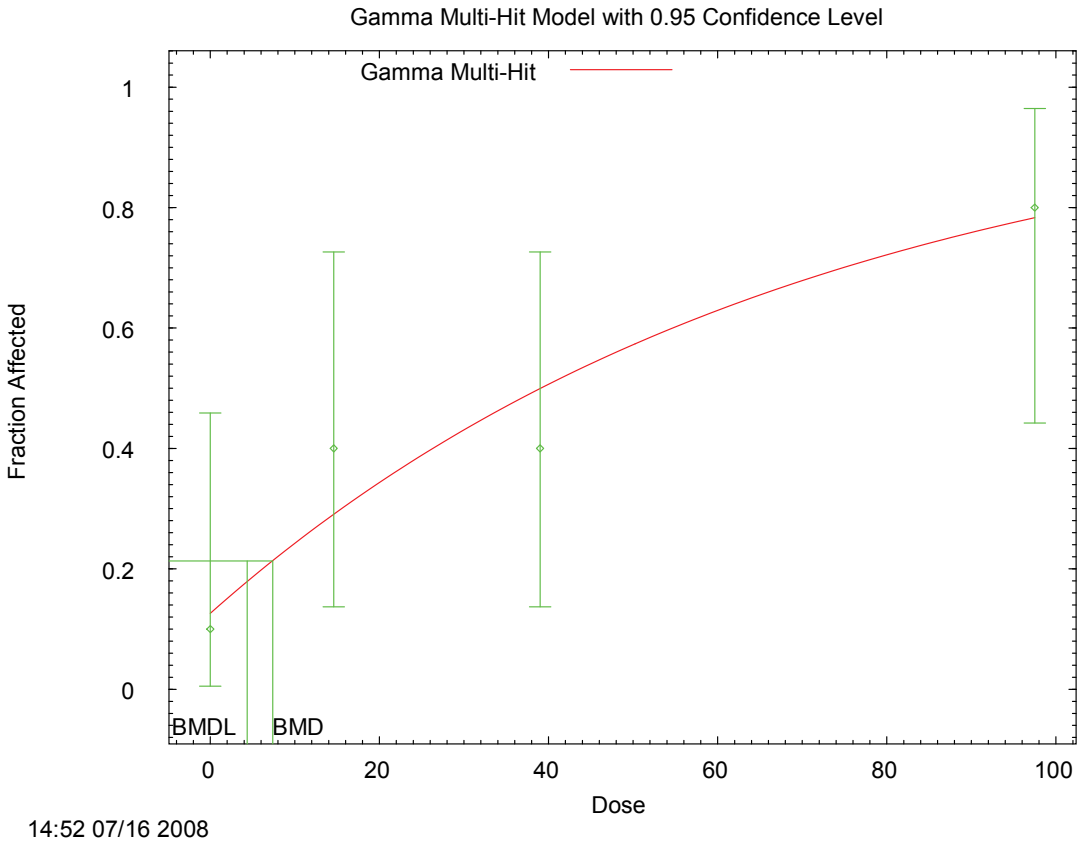

Figure B-4. Representative Best Fitting Model for Vacuolation/Microcysts in Nasal Olfactory Epithelium in Female Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.

MODEL-FITTING RESULTS FOR INCIDENCE OF ATROPHY OF NASAL OLFACTORY EPITHELIUM IN MALE RATS (WIL Research Laboratories, 2002)

All but the probit and logistic models provide adequate fit (see Table B-5). The 1-degree multistage and quantal linear models have the lowest AIC values and provide identical fit to the data; the BMDL value from these models is chosen to represent the data set. The quantal linear model is representative of these models (see Figure B-5).

Table B-5. Model Predictions for Incidence of Atrophy of Nasal Olfactory Epithelium in Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	2	3.94	0.1398	34.5264	14.0015	5.29409
Logistic	2	7.91	0.0192	39.0046	NA[b]	NA
Log-logistic (slope ≥ 1)	2	3.21	0.2008	33.7213	15.1826	4.36048
Log-probit (slope ≥ 1)	2	3.11	0.2111	33.4581	16.4607	9.09944
Multistage (degree = 1, betas ≥ 0)	**3**	**3.75**	**0.2900**	**33.1399**	**7.86439**	**5.03062**
Multistage (degree = 2, betas ≥ 0)	2	3.88	0.1436	35.111	8.72496	5.04195
Multistage (degree = 3, betas ≥ 0	2	3.88	0.1436	35.111	8.72496	5.04195
Probit	2	7.76	0.0206	38.5262	NA	NA
Weibull (power ≥ 1)	2	3.94	0.1392	34.7729	11.9249	5.182
Quantal Linear	**3**	**3.75**	**0.2901**	**33.1399**	**7.86432**	**5.03062**

[a]WIL Research Laboratories, 2002
[b]NA = Not Applicable; model does not provide adequate fit

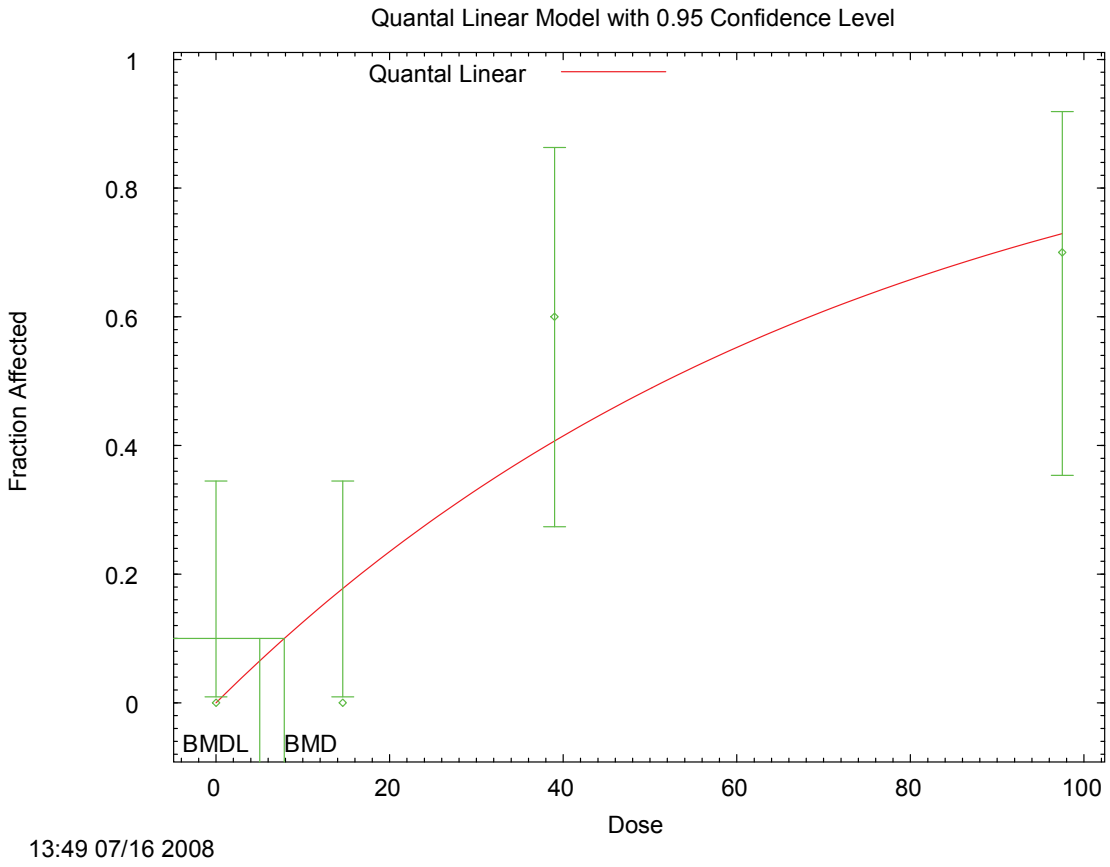

Figure B-5. Representative Best Fitting Model for Atrophy of Nasal Olfactory Epithelium in Male Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.

MODEL-FITTING RESULTS FOR INCIDENCE OF ATROPHY OF NASAL OLFACTORY EPITHELIUM IN FEMALE RATS (WIL Research Laboratories, 2002)

All but the Weibull model provide adequate fit (see Table B-6). The log-logistic model has the lowest AIC value (see Figure B-6).

Table B-6. Model Predictions for Incidence of Atrophy of Nasal Olfactory Epithelium in Female Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value	AIC	BMD_{10ADJ} (mg/m^3)	$BMDL_{10ADJ}$ (mg/m^3)
Gamma (power ≥ 1)	3	0.01	0.9998	14.2324	25.07	13.3745
Logistic	2	0.00	1.0000	16.2173	35.2969	15.2877
Log-logistic (slope ≥ 1)	**3**	**0.00**	**1.0000**	**14.2173**	**32.9312**	**14.2601**
Log-probit (slope ≥ 1)	2	0.00	1.0000	16.2173	29.2977	13.9644
Multistage (degree = 1, betas ≥ 0)	3	5.61	0.1320	23.607	4.25009	2.72382
Multistage (degree = 2, betas ≥ 0)	3	1.74	0.6274	17.2572	12.838	6.59393
Multistage (degree = 3, betas ≥ 0)	3	0.65	0.8860	15.4208	17.8769	8.99183
Probit	2	0.00	1.0000	16.2173	31.9657	14.261
Weibull (power ≥ 1)	Model does not run					
Quantal Linear	3	5.61	0.1320	23.607	4.25009	2.72382

[a] WIL Research Laboratories, 2002

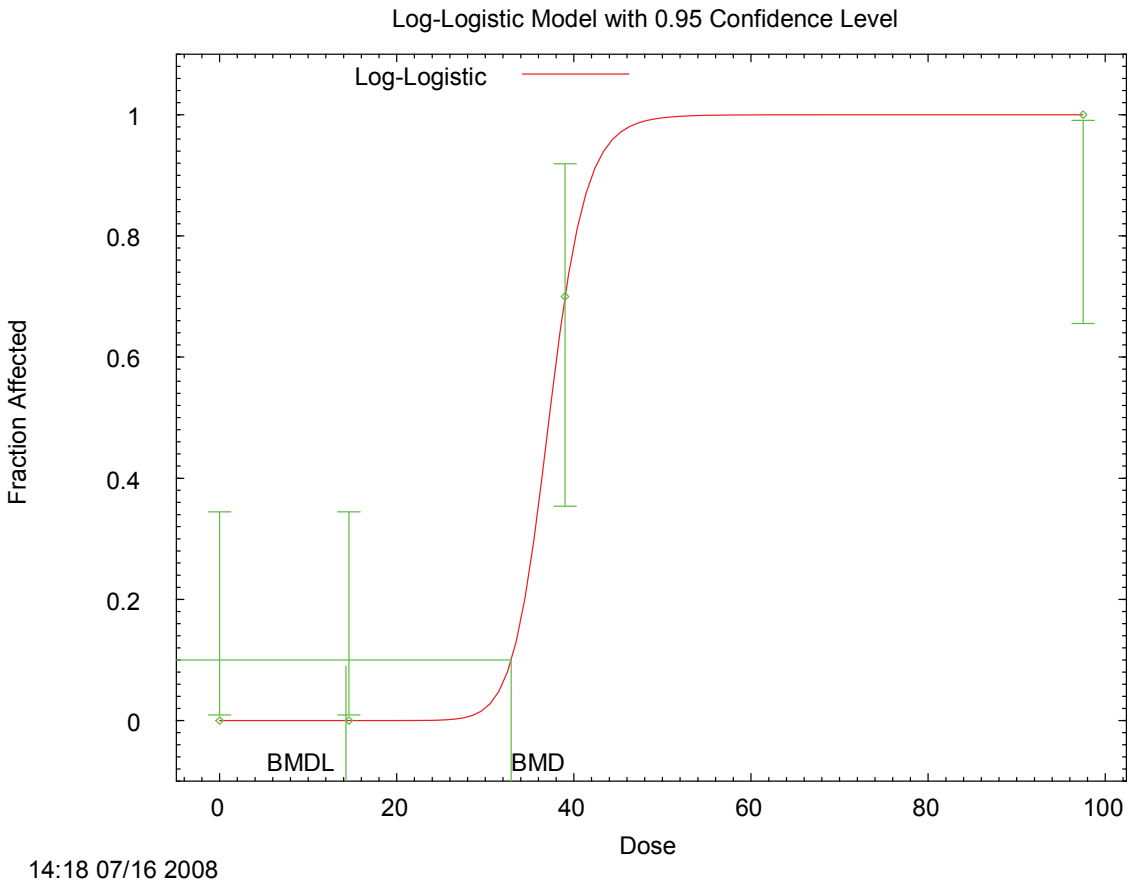

Figure B-6. Best Fitting Model for Atrophy of Nasal Olfactory Epithelium in Female Rats (WIL Research Laboratories, 2002)

Dose is duration-adjusted and in units of mg/m^3.