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# Provisional Peer Reviewed Toxicity Values for

# 1-Chlorobutane

(CASRN 109-69-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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## Acronyms and Abbreviations

| | |
|---|---|
| bw | body weight |
| cc | cubic centimeters |
| CD | Caesarean Delivered |
| CERCLA | Comprehensive Environmental Response, Compensation and Liability Act of 1980 |
| CNS | central nervous system |
| cu.m | cubic meter |
| DWEL | Drinking Water Equivalent Level |
| FEL | frank-effect level |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| g | grams |
| GI | gastrointestinal |
| HEC | human equivalent concentration |
| Hgb | hemoglobin |
| i.m. | intramuscular |
| i.p. | intraperitoneal |
| i.v. | intravenous |
| IRIS | Integrated Risk Information System |
| IUR | inhalation unit risk |
| kg | kilogram |
| L | liter |
| LEL | lowest-effect level |
| 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 |
| m | meter |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mg/kg | milligrams per kilogram |
| mg/L | milligrams per liter |
| MRL | minimal risk level |

| | |
|---|---|
| MTD | maximum tolerated dose |
| MTL | median threshold limit |
| NAAQS | National Ambient Air Quality Standards |
| 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** |
| PBPK | physiologically based pharmacokinetic |
| ppb | parts per billion |
| ppm | parts per million |
| **PPRTV** | **Provisional Peer Reviewed Toxicity Value** |
| RBC | red blood cell(s) |
| RCRA | Resource Conservation and Recovery Act |
| RDDR | Regional deposited dose ratio (for the indicated lung region) |
| REL | relative exposure level |
| RfC | inhalation reference concentration |
| RfD | oral reference dose |
| RGDR | Regional gas dose ratio (for the indicated lung region) |
| s.c. | subcutaneous |
| SCE | sister chromatid exchange |
| SDWA | Safe Drinking Water Act |
| sq.cm. | square centimeters |
| TSCA | Toxic Substances Control Act |
| UF | uncertainty factor |
| µg | microgram |
| µmol | micromoles |
| VOC | volatile organic compound |

10-04-2005

# PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 1-CHLOROBUTANE (CASRN 109-69-3)

## Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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 HEAST (U.S. EPA, 1997) lists a chronic oral RfD of 4E-1 mg/kg-day for 1-chlorobutane, based on a duration-adjusted NOAEL of 43 mg/kg-day for increased mortality, and effects on the central nervous and hematologic systems in a 2-year bioassay in rats (NTP, 1986) and an uncertainty factor of 100. The subchronic RfD of 9E-1 is based on a duration-adjusted NOAEL of 86 mg/kg-day for decreased body weight gain, changes in hematopoiesis, and central nervous system effects in a 13-week study in rats (NTP, 1986) and an uncertainty factor of 100. The source document for both of these RfDs was a Health and Environmental Effects Document (HEED) for Monochlorobutanes (U.S. EPA, 1988). IRIS (U.S. EPA, 2005a) does not list an RfD for 1-chlorobutane, and this chemical is not included in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002). In addition to the Health and Environmental Effects Document (HEED) (U.S. EPA, 1988), the Chemical Assessments and Related Activities

(CARA) list (U.S. EPA, 1991, 1994) reports a Health and Environmental Effects Profile (HEEP) for Monochlorobutanes (U.S. EPA, 1983). ATSDR (2003) has not published a Toxicological Profile for 1-chlorobutane, and no Environmental Health Criteria Document is available (WHO, 2003).

No RfC for 1-chlorobutane is listed in the HEED (U.S. EPA, 1988), HEAST (U.S. EPA, 1997) or IRIS (U.S. EPA, 2005a). ACGIH (2003), NIOSH (2003), and OSHA (2003) have not developed occupational exposure limits for 1-chlorobutane.

1-Chlorobutane is categorized in cancer weight-of-evidence group D (not classifiable as to human carcinogenicity) in the HEED (U.S. EPA, 1988). The HEAST (1997) does not report the carcinogenicity assessment for 1-chlorobutane, but the group D classification is included on IRIS (U.S. EPA, 2005a). IARC (2003) has not evaluated the carcinogenicity of 1-chlorobutane. NTP (1986) has conducted a 2-year carcinogenicity bioassay of 1-chlorobutane in mice and rats, and reported no evidence of carcinogenicity in males or females of either species.

Literature searches were conducted from 1987 through October, 2003 for studies relevant to the derivation of provisional toxicity values for 1-chlorobutane. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB, GENETOX, and CANCERLIT.

## REVIEW OF PERTINENT DATA

### Human Studies

Studies examining the toxicity or carcinogenicity of 1-chlorobutane in humans were not located.

### Animal Studies

In a dose range-finding study sponsored by the National Toxicology Program (NTP, 1986), groups of 10 male and 10 female F344/N rats were given 0, 30, 60, 120, 250, or 500 mg/kg of 1-chlorobutane and groups of 10 male and 10 female B6C3F1 mice were given 0, 60, 120, 250, 500, or 1000 mg/kg of 1-chlorobutane. Each group was treated by gavage with pure compound in corn oil, 5 days/week for 13 weeks. The animals were observed for clinical signs two times per day; moribund animals were killed. For the NTP studies summarized here, if convulsions occurred, they were generally observed at the time of gavage dosing, although this was not clearly specified. Animals were weighed weekly, and extensive histological examinations were performed.

In rats, 6/10 males in the 500 mg/kg group died prematurely (NTP, 1986). Because of increased irritability of rats at the higher doses, dosing by gavage became extremely difficult; three deaths were due to gavage accidents. Survival was 100% in all other groups of rats. A dose-related decrease in weight gain occurred in male and female rats; males in the 250 and 500 mg/kg groups had final weights that were 11 and 20% lower than control weights, respectively, and females in the 500 mg/kg group had weights that were 10% lower than the female control weights. Convulsions occurred in 5/10 male and 2/10 female rats in the 250 mg/kg group, and in 9/10 males and 8/10 females in the 500 mg/kg group. Extramedullary hematopoiesis of the spleen occurred in 3/10 male rats in the 500 mg/kg group and in 0/10 rats in the control groups; the severity was mild in two rats and moderate in the third. No other compound-related clinical signs or histopathological effects were reported for rats.

A number of gavage accidents occurred during the studies using mice (two vehicle control females, a male and female in the 60 mg/kg groups, a female in the 120 mg/kg group, and two females in the 1000 mg/kg group); these accidents were attributed to technician error, rather than any compound-related difficulties (NTP, 1986). No treatment-related changes in body weight were seen in male or female rats of any group. In the 1000 mg/kg group, convulsions occurred in two female mice. No other compound-related clinical signs or histopathological effects were reported for mice.

NTP (1986) also conducted a 2- year toxicology and carcinogenesis study of 1-chlorobutane in male and female F-344/N rats and B6C3F1 mice. In the rat study, groups of 50 animals/sex/group were given 0, 60, or 120 mg/kg of 1-chlorobutane (99.5% pure) in corn oil by gavage 5 days/week for 103 weeks. Animals were observed twice daily, and clinical signs were recorded once per week. Body weights were recorded once per week for the first 12 weeks of the study and once per month thereafter. A necropsy was performed on all animals, including those found dead, unless they were excessively autolyzed or cannibalized. Examinations for grossly visible lesions were performed on all major organs, and pathology was performed on 28 organs, as well as any noticeable gross masses. Sentinel rats were found to have antibodies to the Sendai and RC viruses, but the impact of the presence of these viruses on the reliability of the study results is not known.

Survival was significantly reduced in high-dose male (17/50 treated vs. 40/50 vehicle control) and female rats (11/50 vs. 35/50), relative to controls; these deaths were considered to be compound-related, and not due to errors in gavage (NTP, 1986). The study authors expressed a concern about decreased study sensitivity, in terms of detecting carcinogenesis, resulting from the mortality in the high dose group. Many dosed rats had tremors and convulsions after being gavaged; the study authors suggested a link between animals that showed convulsions and those that died, although supporting incidence data were not provided. Mean body weights of treated and control rats were comparable throughout the study; a slight decrease (3%) in body weight throughout the study in high-dose male rats was not considered to be a treatment-related effect.

Nephropathy occurred in female rats, but did not occur in a dose-related manner and was not accompanied by other evidence indicating that it was a compound-related adverse effect. Cytoplasmic vacuolization of the adrenal occurred in a dose-related manner in male rats; although this effect indicates a build-up of fatty deposits, the toxicological significance of this effect is not clear. Lung alveolar and brain hemorrhage, lymphoid depletion of the spleen, splenic hemosiderosis, and multiple organ congestion occurred in a dose-related manner in male and female rats; in most cases, the differences were only significant at the highest exposure level. Generally, these effects were restricted to rats that died during the study; the study authors suggested that many of these lesions were consistent with rats dying suddenly during convulsions. The incidence of each of these effects was significant when compared with control groups at a dose level of 120 mg/kg, but not at 60 mg/kg.

Pheochromocytomas of the adrenal gland were significantly increased in the low-dose female rats (1/50, vehicle control; 6/50, low-dose; and 1/49, high-dose) (NTP, 1986). The incidence of medullary hyperplasia, an expected preneoplastic observation associated with these tumors (observed in 3/50 vehicle controls; 7/50 low-dose females; and 4/49 high-dose females) did not suggest a dose-related neoplastic relationship. The incidence of pheochromocytomas was low, not dose-related, and not seen in male rats. Furthermore, pheochromocytomas are late-developing tumors and they were not considered by the study authors to be treatment related. Thus, NTP concluded that there was no evidence of carcinogenicity of 1-chlorobutane for male and female rats under the conditions of these studies. It was noted, however, that the chemical-induced mortality in high-dose rats suggests that toxic levels were reached and might have reduced the sensitivity of the study for determining carcinogenicity.

In the mouse portion of the study, groups of 50 male and female B6C3F1 mice were gavaged with 1-chlorobutane (99.5% pure) in corn oil at 0, 500, or 1000 mg/kg-day, 5 days/week for 103 weeks (NTP, 1986). Because of high treatment-related mortality, all mice dosed at 1000 mg/kg-day were sacrificed in the 45th week and a second study with additional groups of 50 mice/sex was started at 0 and 250 mg/kg-day. Animals were observed twice daily, and clinical signs were recorded once per week. Body weights were recorded once per week for the first 12 weeks of the study and once per month thereafter. A necropsy was performed on all animals, including those found dead, unless they were excessively autolyzed or cannibalized. Examinations for grossly visible lesions were performed on all major organs, and pathology was performed on 29 organs, as well as any noticeable gross masses. Sendai virus was present in some female mice in the first study, but not in the second. In addition, mouse hepatitis virus (MHV) was detected in both groups of mouse control animals, but the impact of the presence of these viruses on the reliability of the study results is not known.

Survival (54-64%) was comparable for vehicle controls and 500-mg/kg-day groups in the first study, and also for vehicle controls and 250-mg/kg-day groups in the second study (50-72%) (NTP, 1986). The 1000-mg/kg-day male mice showed lower (~10%) mean body weights,

compared with vehicle controls, after week 36; body weights for other groups were comparable to controls. Compound-related signs included convulsions, primarily in high-dose (1000 mg/kg-day) mice. As with rats, animals dying early often showed hemorrhage of the brain and/or lung. Both control and treated female mice developed suppurative inflammation, with some evidence of *Klebsiella pneumoniae* infection, but the incidence was not elevated by dose. No other effects on noncarcinogenic endpoints were reported in mice.

An increased incidence of alveolar/bronchiolar adenomas or carcinomas (combined) (as evaluated by the Incidental Tumor Test) was observed in females in the 500 mg/kg group (9/50) compared with its vehicle controls (3/50), and no effect was seen in the 250 mg/kg group (8/50 treated vs. 6/50 vehicle control)(NTP, 1986). The incidence of these tumors was not statistically significantly elevated when treated groups were compared with pooled vehicle control groups (9/100) from the first and second part of the study. In addition, the lack of hyperplasia in females and the negative trend seen in males suggest that these marginal effects were not treatment-related. A statistically significantly increased incidence of hepatocellular adenomas or carcinomas (combined) was observed in females in the 500 mg/kg group (8/50 vs. 3/50) but not in the 250 mg/kg group (9/50 vs. 7/50). When compared with pooled vehicle controls from the two studies, however, the incidence was not statistically significantly elevated. In the first study, there was an increased incidence (not statistically significant) of hemangiosarcomas in males (1/50, control; 3/50, 500 mg/kg-day; 4/50, 1000 mg/kg-day), but such an increase was not observed in males in the second study (4/50 control vs. 2/50 at 250 mg/kg); the increase was not statistically significant when treated animals were compared with pooled vehicle controls. Since the incidences of hepatocellular adenomas and carcinomas in females were highly variable between the vehicle controls in the two studies (2-16%) and there were no dose-related effects in male mice, these tumors in female mice were not considered treatment-related. The hemangiosarcomas in male mice were also not considered to be compound-related, as the incidence in the vehicle controls was highly variable (2-8%) and the incidence in the first study was lower than the NTP historical incidence (4%). NTP concluded that there was no evidence of carcinogenicity of 1-chlorobutane for male and female mice under the conditions of these studies.

Poirier et al. (1975) gave groups of 10 male and 10 female strain A/Heston mice a total of 24 i.p. injections (3 injections/week for 8 weeks) of 13, 32, or 65 mmol/kg (1194, 3000, or 6017 mg/kg) of 1-chlorobutane in tricaprylin. Untreated and tricaprylin-treated mice were used as negative controls, and urethane-treated mice were used as positive controls. Mice were sacrificed 24 weeks after the first injection. Survival at termination of the study was >90%. No statistically significant increase in the average number of lung tumors per mouse occurred in mice given 1-chlorobutane. This assay scores only lung tumors and is considered to be a short-term *in vivo* screening test.

Two studies from the Soviet literature were located, but did not provide sufficient information to allow independent evaluation. In one study, groups of 15 rats were dosed orally

with 0, 0.02, 0.2, or 2 mg/kg of 1-chlorobutane in oil for 6 months (Tomashevskaya and Zholdakova, 1979). The frequency of administration was not stated in the translation. At 2 mg/kg, the activities of blood alkaline phosphatase, cholinesterase, and succinate dehydrogenase were altered, and higher blood levels of inorganic phosphate were observed. At 0.02 and 0.2 mg/kg, no statistically significant differences were observed in treated animals. In a second study, groups of 10 rats were given daily oral doses of 0, 0.00022, 0.0022, 0.022, or 110 mg/kg of 1-chlorobutane in sunflower oil for 30 days (Rudnev et al., 1979). A dose-related increase in the titre of antibodies to liver tissue was observed (numerical data not reported), being highest in the 110 mg/kg group and absent in the 0.00022 mg/kg group. A significant increase in the degree of basophil degranulation in the peripheral blood was reported for rats in groups treated with doses $\geq$ 0.0022 mg/kg, and persisted until 8 weeks after treatment when the study was discontinued. After 30 days, a dose-related increase in antibody sensitization and an increased autoimmune patch formation in the peripheral blood occurred in rats given 0.0022, 0.022, or 110 mg/kg of 1-chlorobutane.

**Other Studies**

When tested in the *Salmonella*/microsomal assay, 1-chlorobutane was nonmutagenic in strains TA98, TA100, TA1535, and TA1537 with and without the addition of hepatic homogenates (Eder et al., 1980, 1982a,b; Barber et al., 1981; Barber and Donish, 1982; Zeiger, 1987, 1990; Zeiger et al., 1987; NTP, 1986). In contrast, Simmon (1981) reported positive results in strain TA100 in the absence of hepatic homogenates; however, no control data were provided. Negative results were obtained in an assay of DNA damage assay in *Escherichia coli* (Fluck et al., 1976). 1-Chlorobutane was negative for DNA double-strand break induction in the alkaline elution assay in rat hepatocytes (Storer et al., 1996). 1-Chlorobutane has given mixed (Myhr et al., 1990) or positive (NTP, 1986) results in the mouse lymphoma L5178Y assay in the absence of S9, but was negative in the presence of S9 (Myhr et al., 1990). Negative results were obtained, both with and without S9, in chromosomal aberration tests in Chinese hamster ovary cells and rat bone marrow cells (Anderson et al., 1990; NTP, 1986; Rudnev et al., 1979), and in tests for sister chromatid exchange in Chinese hamster ovary cells (Anderson et al., 1990; NTP, 1986).

## DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1-CHLOROBUTANE

**Subchronic p-RfD**

Only one adequate evaluation of the subchronic toxicity of 1-chlorobutane was located in the literature. NTP (1986) reported that rats exposed to 250 mg/kg-day or greater for 13 weeks showed significant, dose-related decreases in body weight, as well as convulsions.

Extramedullary hematopoiesis of the spleen was noted in male rats exposed to 500 mg/kg-day. Also at 500 mg/kg-day, a number of rats died (some directly due to the chemical and some by gavage error related to increased irritability of the animals). In mice, convulsions were seen only at 1000 mg/kg-day. In support of the neurological findings in the subchronic study, clinical signs and histopathological lesions indicative of a gross neurological effect were also observed in the subsequent chronic rat and mouse studies. In the subchronic rat study, no effects were reported at 120 mg/kg-day or below. There is some uncertainty associated with this finding, however, because systematic tests for sensitive neurological endpoints were not conducted. This is an important issue for this chemical, since gross neurological effects were among the most sensitive effects observed in the study.

Because both changes in body weight and appearance of convulsions were associated with exposure to 250 mg/kg-day, the lowest dose at which effects occurred in the subchronic rat study, both endpoints were modeled using U.S. EPA's Benchmark Dose Software, version 1.3.2. Models suitable for continuous variables were applied to the body weight data shown in Table 1. For convulsions, models suitable for dichotomous variables were applied to data for the incidence of rats that experienced one or more convulsions at any time of the study (see Table 1). A 10% change from control values was used as the benchmark response in either case (U.S. EPA, 1996, 2000). Results were based on extra risk. As males appeared to be most sensitive for both endpoints, only male data were modeled. Results from the various model types are presented in Table 2.

As can be seen from Table 2, the continuous models did not result in adequate model fits for the body weight data using the recommended value of $p>0.1$ (U.S. EPA, 1996, 2000). All of the dichotomous models produced adequate fits ($p>0.1$) to the convulsion incidence data. The best fitting model, as determined by Akaike's Information Criteria (AIC), is the Gamma model. The Gamma model estimated a BMDL of 97 mg/kg-day and BMD of 156 mg/kg-day. In accordance with U.S. EPA (2000) guidance, the BMDL of 97 mg/kg-day was used as the point of departure for derivation of the subchronic p-RfD.

Table 1. Data from the Subchronic NTP (1986) Rat Study Used for BMD Modeling

| Dose Group | N | Final Body Weight | | Number of Animals With Convulsions |
|---|---|---|---|---|
| | | Mean | Standard Deviation | |
| 0 | 10 | 299 | 4 | 0 |
| 30 | 10 | 300 | 5 | 0 |
| 60 | 10 | 290 | 4 | 0 |
| 120 | 10 | 285 | 3 | 0 |

| | | | | |
|---|---|---|---|---|
| 250 | 10 | 265 | 4 | 5 |
| 500 | 10 | 240 | 10 | 9 |

Table 2. BMD Modeling Results for 1-Chlorobutane Based on the Subchronic NTP (1986) Rat Study

| Endpoint | Model | $LED_{10}$ | $ED_{10}$ | P-Value | AIC |
|---|---|---|---|---|---|
| Body Weight | Linear | 231 | 244 | <0.05 | -- |
| Body Weight | Polynomial | 186 | 211 | <0.05 | -- |
| Body Weight | Power | 231 | 244 | <0.05 | -- |
| Body Weight | Hill | 68 | 89 | <0.05 | -- |
| Convulsions | Gamma | 97 | 156 | .8928 | 25.82 |
| Convulsions | Quantal-Quadratic | 88 | 111 | .8429 | 25.93 |
| Convulsions | Weibull | 86 | 144 | .7634 | 26.91 |
| Convulsions | Probit | 108 | 161 | .5318 | 28.03 |
| Convulsions | Logistic | 112 | 163 | .4475 | 28.53 |
| Convulsions | Multi-Stage | 84 | 150 | .5268 | 29.18 |
| Convulsions | Quantal-Linear | 31 | 47 | .1702 | 34.82 |

The BMDL was duration adjusted as follows:

$$BMDL = BMDL \times \frac{5 days / week}{7 days / week}$$
$$= 97 \times 5/7$$
$$= 69\ mg/kg-day$$

To the duration-adjusted BMDL of 69 mg/kg-day, an uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for intrahuman variability, and 10 for inadequacies in the database), was applied to give the provisional **subchronic RfD of 0.07 mg/kg-day**. A full uncertainty factor of 10 was applied for database uncertainties due to the lack of reproductive and developmental data and a lack of evaluation of sensitive neurologic effects in the principal study.

subchronic p-RfD = $LED_{10}$ ÷ UF
= 69 mg/kg-day ÷ 1000
= 0.07 or 7E-2 mg/kg-day

Confidence in the principal study is low-to-medium. The study was an adequate, subchronic study in both sexes of two rodent species that clearly identified a NOAEL and LOAEL; however, reporting of the results was limited (lack of numerical data for many evaluated endpoints), and the study did not adequately evaluate neurological endpoints, which appear to be an important target for 1-chlorobutane. Confidence in the database is low; the only adequate supporting data for the principal subchronic study come from the chronic study described in the same report. Low confidence in the provisional subchronic RfD results.

**Chronic p-RfD**

The only available chronic data on the toxicity of 1-chlorobutane are the data from the NTP (1986) 2-year bioassay. This study identified a NOAEL of 60 mg/kg-day and LOAEL of 120 mg/kg-day in rats for convulsions and tremors, lung and brain hemorrhage, splenic lymphoid depletion and hemosiderosis, multiple organ congestion, and increased mortality in both sexes of rats. The study authors suggest that many of the observed lesions may be related to the convulsions seen following exposure; however, data specifically correlating these effects with animals that showed convulsions or animals that died prior to study termination are not available. Convulsions were also observed (at higher doses) in the chronic mouse study and subchronic rat and mouse studies. There is some uncertainty associated with the NOAEL of 60 mg/kg-day because systematic tests for sensitive neurological endpoints were not conducted. This is an important issue for this chemical, since gross neurological effects were the most sensitive effects observed in the study. Benchmark dose modeling (U.S. EPA, 1996, 2000) was considered for analysis of the chronic rat data, but was not applied because the available data are insufficient to adequately describe the dose-response function (the data from the study identify only one effect level). As such, modeling the data would not reduce the uncertainty regarding identification of the point of departure. As the data are not amenable to Benchmark Dose analysis, a NOAEL/LOAEL approach was adopted.

The NOAEL of 60 mg/kg-day was duration-adjusted as follows:

$$NOAEL_{[ADJ]} = NOAEL \times \frac{5 days / week}{7 days / week}$$

$$= 60 \times {}^{5}\!/_{7}$$

$$= 43 mg/kg - day$$

To the duration-adjusted NOAEL of 43 mg/kg-day, an uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for intrahuman variability, and 10 for inadequacies in the

database, including a lack of evaluation of reproductive, developmental, and sensitive neurological effects) was applied to give the provisional **chronic RfD of 0.04 mg/kg-day**.

| | | |
|---|---|---|
| p-RfD | = | NOAEL ÷ UF |
| | = | 43 mg/kg-day ÷ 1000 |
| | = | 0.04 or 4E-2 mg/kg-day |

Confidence in the principal study is low-to-medium. The study was an adequate, lifetime study in both sexes of two rodent species that clearly identified a NOAEL and LOAEL; however, the likely presence of the Sendai and RC viruses in the rats somewhat confounds study interpretation, the study's ability to identify chronic effects may have been affected by study mortality, and the study's ability to describe the dose-response function of 1-chlorobutane is limited by the fact that only one effect level was identified. Confidence in the database is low; the only adequate supporting data for the principal chronic study come from the subchronic study described in the same report. Low confidence in the provisional chronic RfD results.

## DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1-CHLOROBUTANE

In the absence of subchronic or chronic data on the inhalation toxicity of 1-chlorobutane in humans or animals, derivation of provisional subchronic or chronic RfC values is precluded.

## DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1-CHLOROBUTANE

NTP (1986) examined the effects of 2-year gavage exposure to 1-chlorobutane on male and female F344/N rats (doses of 60 or 120 mg/kg for 5 days/week) and B6C3F1 mice (doses of 250 or 500 mg/kg for 5 days/week). Despite exceeding the MTD, as evidenced by increased high-dose mortality, no consistent evidence of dose-related tumor formation was reported in either sex of either species. The study authors noted that toxicity in high-dose rats, particularly females, reduced the sensitivity of the study for determining carcinogenicity. In a short-term assay screening assay, Poirier et al. (1975) reported that administration of 24 intraperitoneal injections (3/week) to mice at levels of 1194, 3000, or 6017 mg/kg did not result in an increase in the average number of lung tumors per mouse. The overwhelming majority of available tests of mutagenicity, DNA reactivity, and clastogenicity of 1-chlorobutane in bacteria and mammalian cells have been negative. Under the guidelines (U.S. EPA 2005b), the data are inadequate for an assessment of human carcinogenic potential of 1-chlorobutane based on negative results in tests of two non-human species (one of which - in rats - had reduced sensitivity due to high mortality in the high-dose group) and evidence of a lack of genotoxicity.

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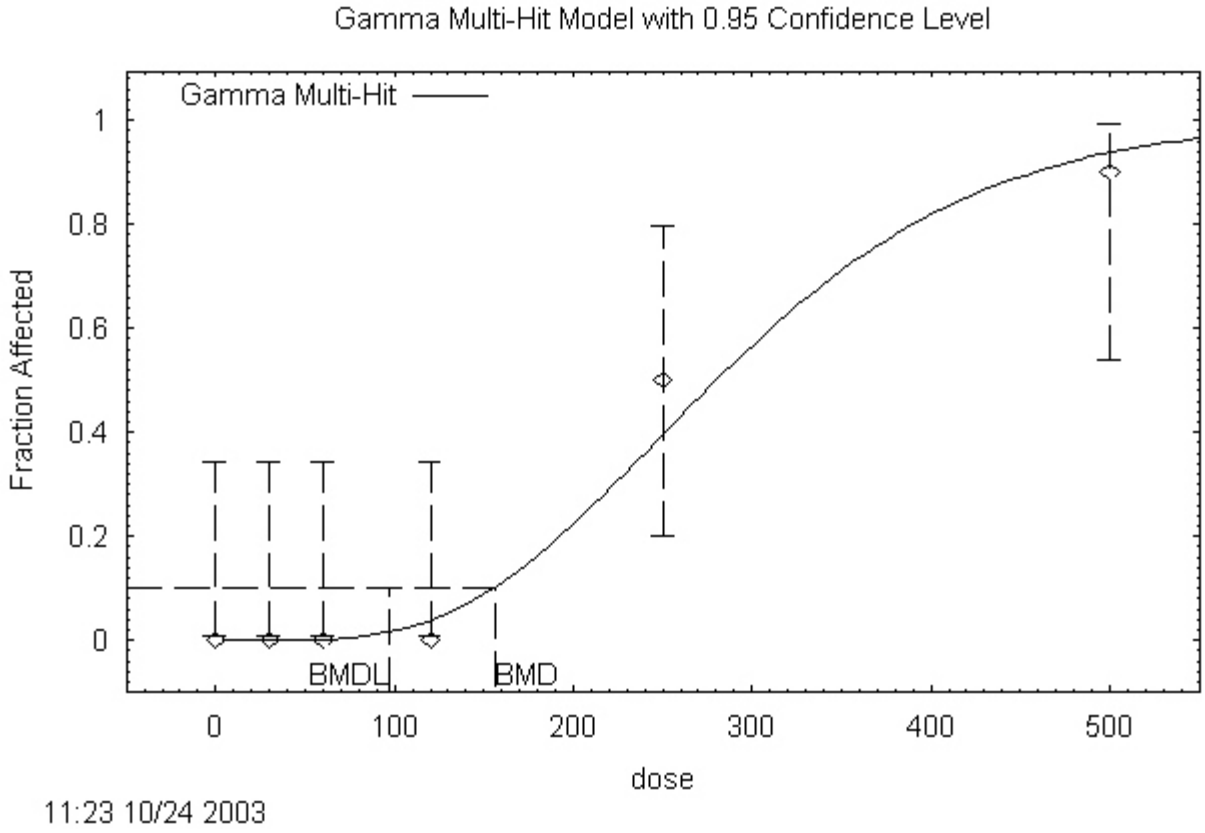
**APPENDIX A - RESULTS OF BENCHMARK DOSE ANALYSIS**



```
==============================================================================
          $Revision: 2.1 $ $Date: 2000/02/26 03:37:57 $
          Input Data File: C:\BMDS\UNSAVED1.(d)
          Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Fri Oct 24 11:23:00 2003
==============================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response]= background+(1-background)*CumGamma[slope*dose,power],
  where CumGamma(.) is the cummulative Gamma distribution function


  Dependent variable = convulsions
  Independent variable = COLUMN1
  Power parameter is restricted as power >=1

  Total number of observations = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



          Default Initial (and Specified) Parameter Values
            Background =    0.0454545
               Slope =    0.0115921
               Power =      3.39562


       Asymptotic Correlation Matrix of Parameter Estimates

       ( *** The model parameter(s)  -Background
            have been estimated at a boundary point, or have been specified by the user,
            and do not appear in the correlation matrix )

             Slope       Power

   Slope          1        0.97

   Power       0.97           1


                  Parameter Estimates

     Variable         Estimate          Std. Err.
   Background                0               NA
      Slope          0.0202592        0.0112356
      Power            6.00738          3.13899
```

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

| Model | Log(likelihood) | Deviance | Test DF | P-value |
|---|---|---|---|---|
| Full model | -10.1823 | | | |
| Fitted model | -10.909 | 1.45348 | 4 | 0.8348 |
| Reduced model | -32.5964 | 44.8281 | 5 | <.0001 |

AIC: 25.8181

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Scaled Size | Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0000 | 0.000 | 0 | 10 | 0 |
| 30.0000 | 0.0000 | 0.000 | 0 | 10 | -0.02024 |
| 60.0000 | 0.0016 | 0.016 | 0 | 10 | -0.1258 |
| 120.0000 | 0.0373 | 0.373 | 0 | 10 | -0.6223 |
| 250.0000 | 0.3942 | 3.942 | 5 | 10 | 0.6847 |
| 500.0000 | 0.9373 | 9.373 | 9 | 10 | -0.4868 |

Chi-square = 1.11 DF = 4 P-value = 0.8928

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 155.846

BMDL = 97.1323