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Provisional Peer Reviewed Toxicity Values for

Benzyl chloride
(CASRN 100-44-7)

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

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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
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

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR BENZYL CHLORIDE (CASRN 100-44-7)

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 new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-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 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

No RfD is available for benzyl chloride on IRIS (U.S. EPA, 2007), in the drinking water standards and health advisories list (U.S. EPA, 2004), or in the Health Effects Assessment Summary Table (HEAST) (U.S. EPA, 1997). The CARA list (U.S. EPA 1991, 1994a) includes a Health and Environmental Effects Profile (HEEP) for benzyl chloride (U.S. EPA, 1986) that did not derive an RfD. The Agency for Toxic Substances and Disease Registry (ATSDR, 2007) and World Health Organization (WHO, 2007) have not derived any oral risk assessment values for benzyl chloride.

No RfC is available for benzyl chloride on IRIS (U.S. EPA, 2007) or in the HEAST (U.S. EPA, 1997). ATSDR (2007) and WHO (2007) have not derived any inhalation risk assessment values for benzyl chloride. ACGIH (2001, 2006) has set a TLV-TWA (threshold limit value–time-weighted average) of 1 ppm (5 mg/m^3) for occupational exposure to benzyl chloride on the basis of acute eye and nasal irritation in humans. The Occupational Safety and Health Administration (OSHA, 2007) PEL (permissible exposure limit) for benzyl chloride is 1 ppm (5 mg/m^3) for an 8-hour TWA. The National Institute of Safety and Health (NIOSH, 2007) recommendations for benzyl chloride include an IDLH (immediately dangerous to life and health) concentration of 10 ppm (52 mg/m^3) and a REL (recommended exposure level) of 1 ppm (5 mg/m^3) as a 15-minute ceiling. The California EPA has established a chronic Reference Exposure Level (REL) of 12 $\mu g/m^3$ for benzyl chloride to protect against respiratory effects (CalEPA, 2005).

A carcinogenicity assessment is available for benzyl chloride on IRIS (U.S. EPA, 2007). Benzyl chloride was assigned to cancer weight-of-evidence Group B2 (*probable human carcinogen*), based on inadequate human data, sufficient evidence in animals and supporting evidence of mutagenicity. An oral slope factor of 1.7E-01 per mg/kg-day and drinking water unit risk of 4.9E-06 per µg/L were derived based on dose-response data for thyroid C-cell adenoma/carcinoma in female rats (Lijinsky, 1986). There is no quantitative estimate of carcinogenic risk from inhalation exposure on IRIS due to inadequate data. The IRIS assessment was verified on 03/01/89 and is based on the 1986 HEEP for benzyl chloride (U.S. EPA, 1986). The HEAST (U.S. EPA, 1997) includes a reference to the carcinogenicity assessment on IRIS.

CalEPA (2007) derived an inhalation unit risk value of 4.9E-5 $(\mu g/m^3)^{-1}$ for benzyl chloride from the EPA oral slope factor of 1.7E-01 per mg/kg-day (U.S. EPA, 2007) by assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg and 100% fractional absorption after inhalation exposure. The ACGIH (2001, 2006) occupational exposure recommendation for benzyl chloride includes an A3 notation (*confirmed animal carcinogen with unknown relevance to humans*). NTP (2007) has not assessed the carcinogenicity of benzyl chloride.

IARC (1982, 1987, 1999) assigned combined exposures to benzoyl chloride and α-chlorinated toluenes (benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride) to Group 2A (*probably carcinogenic to humans*). This classification is based on limited evidence in humans for the carcinogenicity of α-chlorinated toluenes and benzoyl chloride, sufficient evidence in animals for the carcinogenicity of benzyl chloride and benzotrichloride, limited evidence in animals for the carcinogenicity of benzal chloride and inadequate evidence in animals for the carcinogenicity of benzoyl chloride. The human data did not allow any differential risk estimation for any of the individual chlorinated toluenes. The assessment of limited evidence for carcinogenicity of benzyl chloride in animals was based on tumor induction in oral, dermal and subcutaneous injection studies.

The present document does not include a cancer assessment for benzyl chloride, as one is available on IRIS.

Literature searches were conducted from the 1960's through May 2008 for studies relevant to the derivation of provisional toxicity values for benzyl chloride. Databases searched include: MEDLINE (including PubMed cancer subset), TOXLINE (Special, including NTIS subfile), BIOSIS, TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

No information was located regarding the oral toxicity or carcinogenicity of benzyl chloride in humans.

Available information on the toxicity of inhaled benzyl chloride in humans consists of a limited secondary report of an occupational study. In the Encyclopaedia of Occupational Health and Safety, Mihajlova (1983) summarized noncancer health effects in workers exposed to 10 mg/m^3 (1.9 ppm) of benzyl chloride. Workers complained of weakness, rapid fatigue, persistent headaches, irritability, anorexia and insomnia. Medical examinations of the workers revealed asthenia, dystonia of the autonomic nervous system, possible disturbances of liver function (increased blood bilirubin, positive Takata-Ara and Weltmann tests), a reduction in the number of leukocytes and an increased tendency to illnesses similar to colds or allergic rhinitis. Additional relevant information, particularly the range and duration of exposure and incidences of adverse effects, was not reported.

Several epidemiology studies investigated cancer mortality in workers occupationally exposed to benzyl chloride and other compounds during the production of benzoyl chloride and other chlorinated chemicals (Hagmar et al., 1986; Sakabe and Fukuda, 1977; Sakabe et al., 1976; Sorahan and Cathcart, 1989; Sorahan et al., 1983; Wong and Morgan, 1984; Wong, 1988). Based on assessments of these studies by EPA in the 1989 carcinogenicity assessment of benzyl chloride on IRIS (U.S. EPA, 2007) and more recently by IARC (1999), the available human data are inadequate for assessing the carcinogenicity of benzyl chloride alone. Study limitations include small numbers of cancer deaths, lack of quantitative exposure data, exposure to multiple chemicals (some of which are known carcinogens) and other confounding factors (e.g., no data on smoking status or lung cancer occurring in smokers only).

Animal Studies

Oral Exposure

In a National Cancer Institute (NCI) subchronic rat study, groups of 10 ten-week-old male and 10 eight-week-old female Fisher 344/N rats were given 0, 15, 30, 62, 125 or 250 mg/kg of benzyl chloride in corn oil by gavage three times a week for 37 weeks (males) or 27 weeks (females) (Bunner and Creasia, 1982; Lijinsky, 1986; Reuber, 1979). Rats were weighed weekly and all survivors were necropsied and all major organs were examined histopathologically; animals that died during treatment were not examined, and the scope of the examinations was not specified. Parallel groups of 4 male and 4 female rats were given 0, 30 or 125 mg/kg of benzyl chloride as above to be used for interim sacrifices at 5, 10 and 15 weeks, but results of these sacrifices were not reported. This study was designed to determine a maximum tolerated dose for a NCI chronic cancer bioassay in rats (Lijinsky, 1986).

Mortality occurred in 0% of males and 60% of females given 62 mg/kg-day and 100% of both sexes at ≥125 mg/kg-day, as detailed in Table 1. Body weight gain was decreased in both sexes at 62 mg/kg-day (amounts not reported, but to a statistically significant degree only in males). Gross pathological findings were not reported. Histopathological changes were found prominently in the squamous stomach (forestomach) and heart. Squamous stomach lesions included hyperkeratosis in males at 15, 62 and 125 mg/kg-day and females at 30 and 62 mg/kg-day, hyperplasia in males at 62 and 125 mg/kg-day and females at 62 mg/kg-day, and acute and chronic gastritis in males and females at ≥125 mg/kg-day (Table 1). Severe acute gastritis and ulceration was the probable cause of death in both sexes at 125 mg/kg-day. However, the

Table 1. Incidences of Stomach and Heart Lesions in Rats Exposed to Benzyl Chloride by Gavage on 3 Days/Week for 27 or 37 Weeks

Dose (mg/kg-day)	Squamous Stomach			Heart		
	Hyperkeratosis	Hyperplasia	Gastritis/ Ulcers[a]	Hyperplasia[b]	Myocardial Necrosis[c]	Edema
Male Rats (10/dose) (37 weeks)						
0	0/10	0/10	0/10	NR	NR	NR
15	2/10	0/10	0/10	almost all rats	most rats[f]	NR
30	0/9	0/9	0/9	almost all rats	most rats[f]	NR
62	6/10	5/10	0/10	almost all rats	most rats[f]	NR
125[d]	5/10	4/10	7/10[k]	some rats	NR	NR
250[e]	0/8	0/8	0/8	some rats	all rats[g]	NR
Female Rats (10/dose) (27 weeks)						
0	1/10	0/10	0/10	NR	NR	NR
15	0/10	0/10	0/10	NR	NR	NR
30	5/10	0/10	0/10	NR	NR	NR
62[h]	5/10	5/10	0/10	NR	4/10	NR
125[i]	0/10	0/10	8/10[k]	NR	NR	NR
250[j]	0/10	0/10	2/10	NR	NR	all rats[l]

NR = not reported but assumed to be zero

[a]Acute and/or chronic gastritis, often with ulcers.

[b]Early lesions consisted of granulation tissue and proliferation of interstitial cells. Later lesions were atypical (not otherwise specified) and a few resembled sarcomas. Incidences not specified.

[c]Focal acute myocardial necrosis.

[d]All animals died within 2-3 weeks.

[e]All animals died within 10 days.

[f]Acute myocardial necrosis was found in most rats at terminal sacrifice. Incidence not specified.

[g]Acute myocardial necrosis was the probable cause of death in males at 250 mg/kg-day. Incidence not specified.

[h]4/10 survived 27 weeks. 1/10 developed basal cell carcinoma *in situ* of the squamous stomach.

[i]All animals died within 8 days.

[j]All animals died within 24 hours.

[k]Severe acute gastritis and ulceration was the probable cause of death in both sexes at 125 mg/kg-day.

[l]Edema of the heart was the probable cause of death in females at 250 mg/kg-day; incidence not specified. Severe congestion and edema of the lungs and liver also occurred in 250 mg/kg-day females (incidences not reported).

Source: Bunner and Creasia, 1982; Lijinsky, 1986; Reuber, 1979

incidence of forestomach lesions was sporadic across the dose groups with no clear dose-related response. Cardiac lesions were observed in most males at all dose levels (Table 1). The earliest cardiac lesions consisted of hyperplastic changes (granulation tissue and proliferation of interstitial cells), and later lesions were atypical (not otherwise specified). The times at which the early and late lesions were observed were not specified. A few of the later cardiac lesions resembled sarcomas (incidence not reported), suggesting that some of the later cardiac lesions might have been malignant (additional information on histology of possible malignant lesions not reported), but the earlier lesions were considered to be noncancerous and relevant to toxicity assessment. Additionally, focal acute myocardial necrosis occurred in most or all treated males at $\geq$15 mg/kg-day (Table 1). The incidence of cardiac lesions in the control animals was not reported but negative results in general were not reported. The control incidence was assumed to be zero, as experimental protocol specified conducting histopathological examinations of all animals. Heart lesion data were not reported for most groups of females (Table 1); the only reported cardiac lesions in females were acute myocardial necrosis at 62 mg/kg-day and edema at 250 mg/kg-day (Table 1); cardiac edema was the probable cause of death in the 250 mg/kg-day females. The high-dose females also had severe congestion and edema of the lungs and liver; histological findings in other tissues were not reported for either sex. The heart was the most sensitive target as shown by hyperplastic and necrotic lesions in male rats at doses as low as 15 mg/kg-day. As incidence was not reported precisely, statistical analysis was not possible. However, the observation of lesions in "most rats" at the lowest dose is sufficient to establish a LOAEL of 15 mg/kg-day for systemic toxicity based on cardiac lesions. A NOAEL was not identified.

In an NCI subchronic mouse study, groups of 10 male and 10 female (C57BL/6J x BALB/c)F_1 mice were given 0, 6.3, 12.5, 25, 50 or 100 mg/kg of benzyl chloride in corn oil by gavage 3 days/week for 26 weeks (Lijinsky, 1986). Mice were weighed weekly and all survivors were necropsied and examined histopathologically; animals that died during treatment were not examined and the scope of the examinations was not specified. Parallel groups of 4 male and 4 female mice were given 0, 12.5 or 50 mg/kg of benzyl chloride as above to be used for interim sacrifices at 5,10 and 15 weeks, but results of the these sacrifices were not reported. This study was designed to determine a maximum tolerated dose for a NCI chronic cancer bioassay (Lijinsky, 1986). No mortality or significant decrease in body weight gain was observed in any group. Histopathologic examinations showed effects only in the liver, consisting of hyperplasia reported as moderate at unspecified lower dose levels, occasionally severe at 50 mg/kg-day and frequently severe at 100 mg/kg-day. Lack of additional information on liver hyperplasia, particularly incidence data, precludes identification of a NOAEL or LOAEL.

In the NCI chronic rat study, groups of 52 male and 52 female F344 rats were given 0, 15 or 30 mg/kg of benzyl chloride in corn oil by gavage 3 days/week for 104 weeks (Lijinsky, 1986). Surviving animals were sacrificed 3-4 weeks after the last dose. Reported endpoints were limited to survival, body weight (measured throughout the study) and histopathology (comprehensive examinations were performed on all animals at terminal sacrifice, as well as on those found dead or moribund). No significant differences in survival, body weight or incidences of non-neoplastic lesions between treated and control groups were reported. Additional information regarding these findings, including incidence data, was not provided. No histopathological findings were reported on microscopic examination of the stomach and heart;

thus, there is no indication that chronic exposure results in the development of the non-neoplastic forestomach and cardiac lesions observed in the subchronic exposure study (Bunner and Creasia, 1982). There was no discussion of the discrepancies between the subchronic and chronic studies. Neoplastic effects included squamous cell tumors of the forestomach in three high-dose males (two with carcinoma, one with papilloma) and statistically significantly increased incidences of thyroid C-cell adenoma/carcinoma in high-dose females (4/52, 8/51 and 14/52 for the control, low- and high-dose). A NOAEL of 30 mg/kg-day, the highest dose tested, was identified for chronic toxicity, but the NOAEL is equivocal due to the incomplete reporting of the non-neoplastic findings.

In the NCI chronic mouse study, groups of 52 male and 52 female (C57BL/6J x BALB/c)F_1 mice were given 0, 50 or 100 mg/kg of benzyl chloride in corn oil by gavage 3 days/week for 104 weeks (Lijinsky, 1986). Surviving animals were sacrificed 3-4 weeks after the last dose. Reported endpoints were limited to survival, body weight (measured throughout the study) and histopathology (comprehensive examinations were performed on all animals at terminal sacrifice, as well as on those found dead or moribund). Treatment with benzyl chloride had no effect on survival or body weight compared to controls. Incidences of several types of tumors were significantly increased in high-dose mice, including forestomach carcinoma/papilloma in males (0/51, 4/52 and 32/52 for control, low- and high-dose) and females (0/52, 5/50, 19/51), hemangioma/hemangiosarcoma in males (0/52, 0/52, 5/52) and lung alveolar-bronchiolar adenoma/carcinoma in females (1/51, 2/51, 6/51). Epithelial hyperplasia occurred in the stomachs of mice without stomach tumors, but incidences and effect levels were not reported. There were no statistically significant increases in incidences of other nonneoplastic lesions (additional information not reported). A lack of additional information on the stomach hyperplasia, particularly incidence data, precludes identification of a NOAEL or LOAEL.

Developmental toxicity was evaluated in groups of 17 female New Zealand albino rabbits that were given 0, 10 or 30 mg/kg-day of benzyl chloride in gelatin capsules on gestation days (GD) 6-18 (Monsanto Co., 1977a). Maternal body weight, mortality and behavioral reactions were assessed through GD 29, at which time the does were sacrificed, implantations and resorptions assessed, and fetuses examined for viability, body weight and external abnormalities. Subsequently, fetal viability in a 37°C incubator was monitored for 24 hours by observing respiratory and paw movements hourly for 7 hours and at hour 24 and then all offspring were examined for internal and skeletal abnormalities. Benzyl chloride exposure had no effect on any of the endpoints, indicating that this study identified a NOAEL of 30 mg/kg-day, but no LOAEL for maternal and developmental toxicity in rabbits.

Developmental toxicity was evaluated in groups of 8 female Sprague-Dawley rats that were given 0, 50 or 100 mg/kg-day of benzyl chloride in corn oil by gavage on GD 6-15 and sacrificed on GD 20 (Skowronski and Abdel-Rahman, 1986). Maternal endpoints included body weight, signs of toxicity and survival. Developmental endpoints included numbers of implantations, resorptions, live and dead fetuses and fetal weight, length, gender, external abnormalities, skeletal abnormalities (half of each litter) and visceral abnormalities (remaining half of each litter). No maternal effects were observed. The only statistically significant ($p<0.05$) developmental effect was a 10% reduction in mean fetal length in the high-dose group;

crown-to-rump lengths (mean ± SE) were 4.0 ± 0.1, 3.9 ± 0.1 and 3.6 ± 0.1 cm at 0, 50 and 100 mg/kg-day, respectively. No major skeletal or visceral abnormalities were observed, although incidences of minor sternebral anomalies (e.g., small, slanted and incompletely ossified sternebrae) were slightly increased (not statistically significant or clearly dose-related) in treated fetuses. This study identified a NOAEL of 100 mg/kg-day and no LOAEL for maternal toxicity and a NOAEL of 50 mg/kg-day and a LOAEL of 100 mg/kg-day for developmental toxicity (minor fetotoxicity manifested as slightly reduced crown-rump length) in rats.

Inhalation Exposure

Groups of 10 male Swiss OF_1 mice were exposed to benzyl chloride vapor at mean measured concentrations of 22 ± 4.2 ppm or 46 ± 8.8 ppm (114 or 238 mg/m^3) for 6 hours/day, 5 days/week for 4, 9 or 14 days (Zissu, 1995). The targeted concentrations were 17 and 51 ppm, which were the RD_{50} and 3 x RD_{50}, respectively. RD_{50} is the concentration at which breathing rate in Swiss mice is decreased by 50% during a 15-minute exposure due to upper respiratory tract sensory irritation (trigeminal nerve stimulation in the nasal mucosa). Groups of five control mice were exposed to filtered air for each benzyl chloride group. Histological examinations were performed on the nasal passages, trachea and lungs. Histology of nonrespiratory tract tissues and other endpoints were not evaluated. The 46 ppm exposure level induced lesions in the nasal anterior respiratory epithelium (rhinitis, metaplasia, necrosis) and olfactory epithelium in the dorsal meatus (extensive loss of sensory epithelium with damage to sustentacular cells). The nasal lesions were collectively graded as severe, very severe and severe after 4, 9 and 14 days of exposure, respectively. No histological changes in the trachea or lungs were observed. The 22 ppm exposure level is considered to be a NOAEL because the sensory irritant response (decreased breathing rate) was not accompanied by any histopathological changes in the upper or lower respiratory tract and the relevance of the mouse RD_{50} test for evaluating respiratory tract irritation in humans is unclear (Bos et al., 1991, 2002). Based on the induction of nasal lesions, this study identified a NOAEL of 22 ppm and LOAEL of 46 ppm for short-term exposure in mice.

Histopathology results are available for a study in which groups of 16 male and 16 female rats (strain not reported) were exposed to an aerosol (uncharacterized) of benzyl chloride at 0, 4.2, 17.6, 45.2 or 167 mg/m^3 (0, 0.8, 3.4, 8.7 or 38.0 ppm) for 4 weeks (Rohm and Haas Co., 1988). The hours/day and days/week of exposure were not indicated and a report of the complete study was not located. Histology evaluations were limited to the nasal cavity including turbinates, larynx, trachea, lungs and thoracic lymph nodes in 10 rats/sex at 0 and 38 ppm and to the nasal turbinates only in the remaining 6 rats/sex at 0 ppm and in all 16 rats/sex at 8.7 ppm. Findings included nasal turbinate lesions in all examined rats at 38 ppm; the mucosa of the anterior nasal turbinates exhibited hyperplasia and non-keratinizing squamous metaplasia, rarely with necrosis or inflammatory cell infiltration. There were no exposure-related histopathological changes in the nasal cavity/turbinates at 8.7 ppm, or in the other parts of the respiratory tract or thoracic lymph nodes at 8.7 or 38 ppm. The limited available information indicates that short-term exposure to 38 ppm caused nasal lesions in rats, but identification of a useful NOAEL or LOAEL is precluded by the incomplete exposure information.

Groups of 5 male and 5 female albino rats were exposed to benzyl chloride vapor in mean analytical concentrations of 0, 14.4, 50.7 or 143.6 ppm (0, 75, 263, or 744 mg/m^3) for 6 hours/day, 5 days/week for 2 weeks (Monsanto Co., 1977b). Endpoints examined were clinical signs, mortality, body weight and gross pathology. Hypoactivity and ptosis reportedly occurred in rats in all three exposure groups (incidence data not reported), but not in unexposed controls. Effects observed at ≥50.7 ppm included salivation, ruffed fur, dyspnea, nasal discharge and weakness (incidences not reported), as well as body weight loss. At 143.6 ppm, rats exhibited tremors and ataxia (incidences not reported) and 2/5 males and 4/5 females died during the second week of exposure. At necropsy, lungs of the 143.6 ppm rats did not collapse when the thoraxes were opened; as noted in another study by these investigators (Monsanto Co., 1977b), this effect is consistent with pulmonary edema. No other effects of exposure were reported. Evaluation of this study is complicated by the small numbers of animals and poorly reported data. The small number of rats and unreported incidence data preclude classifying the low (14.4 ppm) exposure concentration as a NOAEL or LOAEL, although 50.7 ppm is a clear adverse effect level based on multiple clinical signs, including nasal discharge and dyspnea.

Groups of 10 male and 10 female Sprague-Dawley rats, 10 male Duncan-Hartley guinea pigs and 10 male Syrian Golden hamsters were exposed to benzyl chloride vapor concentrations of 0, 12, 35 or 102 ppm (0, 60, 180 or 530 mg/m^3) for 6 hours/day, 5 days/week for 5 weeks (24 exposure days) (Monsanto Co., 1983). Endpoints evaluated in all species included clinical signs, mortality, body weight and gross pathology. Histopathologic examinations were conducted only in guinea pigs and limited to the lungs in two animals per group from the control, mid- and high-level groups.

In the rat 5-week study, exposure-related adverse effects were observed only at the highest exposure level (102 ppm) (Monsanto Co., 1983). All high-level male and female rats had symptoms of respiratory difficulties (sneezing and congested breathing) during exposure and two high-exposure males additionally experienced rapid or shallow breathing, but no clinical signs were observed in the low- and mid-level groups. No eye irritation or other exposure-related clinical signs or gross lesions were observed in any group. Body weight gain was significantly reduced in high-level males throughout the study (final weight was 20.6% lower than controls, $p \leq 0.01$) and in high-level females at week 1 and weeks 3-5 (final weight was 13.9% lower than controls, $p \leq 0.01$), but low- and mid-level group body weights were comparable to controls. This study identified a NOAEL of 35 ppm and LOAEL of 102 ppm in rats based on respiratory symptoms and decreased body weight gain.

In the guinea pig 5-week study, clinical signs that included labored breathing, sneezing, eye irritation, lacrimation and wetness around the nose and mouth and/or chest and feet occurred in all animals at 102 ppm (Monsanto Co., 1983). There were no clear exposure-related clinical signs at lower concentrations or significant changes in body weight at any exposure level. At necropsy, incidences of gross lesions were increased in the lungs in the mid- and high-concentration groups; these pulmonary effects consisted of edematous changes and hemorrhage(s) in the affected animals (Table 2). In afflicted animals, the lungs failed to collapse and, when incised, released a thin watery clear or off-white fluid; these effects were tentatively attributed to diffuse mild pulmonary edema. Lungs from two affected animals from each of the mid- and high-concentration groups and lungs from two animals in the control group were

Table 2. Incidence of pulmonary effects in guinea pigs exposed to benzyl chloride by inhalation for 5 weeks (6 hours per day, 5 days per week)

Nominal exposure level in ppm (mg/m^3)	0	12 (60)	35 (80)	102 (530)
edema	0/10 [a]	1/10	5/10	5/10
hemorrhage	1/10	0/10	3/10	2/10

[a] number affected/number exposed
Source: Monsanto Co., 1983

examined for histopathology. The most prominent exposure-related microscopic lesion was diffuse distension of the alveoli with thinning of the bordering interstitium. Small foci of pulmonary emphysema and very mild edema were observed occasionally at the high concentration, but the edema was considered by the investigators to be of insufficient severity to have caused the gross lesion. The smooth muscle surrounding bronchioles and bronchi was moderately thickened. The lungs of the single low-exposure level animal showing gross pulmonary signs were not examined microscopically. According to the investigators, the results of this study suggest that 12 ppm was a no effect level and that exposure to $\geq$35 ppm initiated changes in pulmonary tissues, because the gross edematous changes were substantiated by histological findings of mild pulmonary edema and more marked alveolar distention, and the finding of gross edema in one animal at 12 ppm may not be related to treatment. This study identified a NOAEL of 12 ppm based on gross lung lesions (histology not evaluated at this concentration) and a LOAEL of 35 ppm based on gross and microscopic lung lesions, in guinea pigs.

In the hamster 5-week study, exposure-related adverse effects were observed only at 102 ppm (Monsanto Co., 1983). Effects included clinical signs of irritation (sneezing and eye irritation) in all animals and significantly reduced body weight gain during weeks 2-5 (final weight was 16.3% lower than controls, $p \leq 0.01$). The most prominent gross lesion apparent at necropsy was abnormal discoloration/pigmentation of the liver, which appeared to be exposure-related; incidences were 2/10, 4/10, 6/10 and 7/10 at 0, 12, 35 and 102 ppm, respectively. The significance of this finding is uncertain because histological examinations were not performed; the researchers considered the lesion to be an artifact of experimental procedures (incomplete exsanguination at necropsy). Gross lung congestion was observed in a few animals but was not clearly exposure-related; incidences were 0/10, 1/10, 0/10 and 2/10 at 0, 12, 35 and 102 ppm, respectively. This study identified a NOAEL of 35 ppm and a LOAEL of 102 ppm in hamsters, based on clinical signs of nasal and eye irritation and decreased body weight gain.

Groups of 30 male and 30 female Sprague-Dawley rats and 30 male Hartley guinea pigs were exposed to mean analytical benzyl chloride vapor concentrations of 0, 0.005, 0.062 or 0.148 mg/L (5, 62 or 148 mg/m^3; 1.0, 12.0 or 28.6 ppm) for 6 hours/day, 5 days/week for 14 weeks (10 animals/group) or 27 weeks (20 animals/group) (Monsanto Co., 1984). Endpoints evaluated throughout the study included clinical signs and body weight. Endpoints evaluated at weeks 14 and 28 included hematology (erythrocyte count, total and differential white blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and

mean corpuscular hemoglobin concentration), serum chemistry (alkaline phosphatase, serum glutamic pyruvic transaminase, total bilirubin, blood urea nitrogen, total protein, potassium and sodium), urine indices (volume, specific gravity, total protein, glucose, pH presence of blood, color and gross appearance), selected organ weights (liver, kidney, adrenal, brain, heart, spleen, pituitary and testis) and gross pathology. Histological examinations were performed on 10 animals/sex/species from the control and high-exposure (28.6 ppm) groups at 27 weeks; due to a lack of compound-related histopathology in these animals, tissue examinations were not performed in the low- and mid-exposure groups at 27 weeks or for any of the animals sacrificed at 14 weeks. The histological examinations included the organs that were weighed, as well as nasal turbinates, trachea, lung, esophagus, stomach, small and large intestines, pancreas, prostate, uterus, ovary, thyroids, parathyroids, aorta, bone, bone marrow, mesenteric lymph nodes, urinary bladder, skeletal muscle, skin, eyes and gross lesions.

In rats, exposure to benzyl chloride had no effect on clinical signs, survival, body weight, serum chemistry or urinalysis (Monsanto Co., 1984). The only statistically significant ($p \leq 0.05$) hematological effect was a slight reduction in mean corpuscular volume (MCV) in female rats at $\geq$12 ppm at week 14 only; MCV was 1.0, 2.9 and 3.0% lower than controls at 1.0, 12.0 and 28.6 ppm, respectively. The small (3.0%) decrease in MCV is not considered clinically significant. Uterine hydrometra at an incidence of 0/10, 0/10, 1/10 and 2/10 for the 0, 5, 60 and 148 mg/m^3 exposure groups, respectively, were reported for the scheduled interim sacrifice at 14 weeks. Statistical significance was not reported, presumably being greater than the $p = 0.05$ criterion. However, a Cochran-Armitage lack-of-trend test performed by the U.S. EPA obtained statistical significance at the $p = 0.03$ level. At terminal sacrifice, uterine hydrometra also were evident at an incidence of 0/20, 2/19, 1/20 and 2/19 for the 0, 5, 60 and 148 mg/m^3 exposure groups, respectively. The Cochran-Armitage lack-of-trend test was suggestive of a trend ($p = 0.15$). The clinical significance of these findings is uncertain. Other effects included organ weight changes at week 27, but with no exposure-related gross pathology or histopathology. Statistically significant changes in organ weights included increased absolute and relative spleen weights in females at 28.6 ppm (14 and 18% higher than controls, respectively), increased relative left kidney weight in females at 28.6 ppm (21% higher than controls; relative weight of right kidney was increased but not statistically significant), decreased relative heart weight in males at $\geq$1.0 ppm (~10% lower than controls at all levels) and decreased absolute heart weight in males at 28.6 ppm (11% lower than controls). The high exposure concentration of 28.6 ppm (148 mg/m^3) is a LOAEL for rats in this study based on the changes in spleen, kidney and heart weights, although somewhat equivocal due to the absence of gross or microscopic pathology or serum chemistry changes.

In guinea pigs, exposure to benzyl chloride had no effect on clinical signs, survival, body weight, serum chemistry or urinalysis (Monsanto Co., 1984). The only statistically significant ($p \leq 0.05$) hematological effect was a slight reduction in MCV in low- and high-exposure guinea pigs at week 27; MCV was 2.5, 1.5 and 5.5% lower than controls at 1.0, 12.0 and 28.6 ppm, respectively. The decreases in MCV are not considered clinically significant due to the small ($\leq$5.5%) magnitudes and lack of other hematological effects. Absolute and relative kidney weights were increased at 28.6 ppm, but the differences were only statistically significant ($p \leq 0.05$) for the left kidney (~10% less than controls for both absolute and relative weights); no gross or histopahtological lesions were reported. An increased incidence of grossly observable

liver lesions was evident at the highest exposure level. Necrotic areas in the liver were reported at an incidence of 1/20, 0/18, 0/20 and 3/19 for the 0, 5, 60 and 148 mg/m^3 exposure groups, respectively. Abnormal pigmentation was present in 2/20, 1/18, 1/20 and 4/19 for the 0, 5, 60 and 148 mg/m^3 exposure groups, respectively. Statistical significance was not reported, presumably being greater than the $p = 0.05$ criterion. However, comparing the high-exposure level necrosis response to the combined response for the three lower exposure groups, statistical significance is obtained ($p = 0.030$) by the Fisher's exact test. A Cochran-Armitage lack-of-trend test yields a p-value of 0.083 level for liver necrosis. For liver pigmentation, the Fisher's exact test ($p = 0.10$) and Cochran-Armitage lack-of-trend test ($p = 0.16$) were only suggestive of an effect. Absolute and relative liver weights also were increased in treated animals compared to controls, with relative weights increased by about 10% in the two highest exposure groups for males ($p \leq 0.01$). Microscopic examination of tissues at terminal sacrifice was performed on only 10 animals of each sex for only the control and high-dose groups. There was no significant difference in the incidence of liver necrosis between control (2/10) and high-dose (3/10) males. Taken together, the observations are suggestive of adverse liver effects at the high exposure level (148 mg/m^3). Accordingly, the exposure level of 148 mg/m^3 is designated as a LOAEL for liver effects in guinea pigs in this 27-week study.

Other Studies

Acute Inhalation Exposure – Acute exposure to benzyl chloride vapor can produce irritation of the eyes and upper respiratory tract in humans. The following dose-response information on inhalation of benzyl chloride vapor, apparently based on limited information, was reported in the NIOSH (1978) criteria document for benzyl chloride and summarized by ACGIH (2001) as follows: exposure to 1.5 ppm for 5 minutes resulted in slight conjunctivitis; 8 ppm was the threshold for eye irritation in a 10-second exposure trial and a single breath of air containing 35 ppm caused nasal irritation.

Changes in neuromuscular excitability were observed in mice during a 3-minute "behavioral despair" swimming test conducted during a 4-hour exposure to 12-22 ppm benzyl chloride (De Ceaurriz et al., 1983).

Dermal and Parenteral Exposure – The carcinogenicity of benzyl chloride has been tested in dermal, subcutaneous and intraperitoneal studies in animals (Ashby et al., 1982; Coombs, 1982a,b; Fukuda et al., 1981). These studies were evaluated by EPA in the 1989 carcinogenicity assessment for benzyl chloride on IRIS (U.S. EPA, 2007); newer cancer studies were not located. As indicated in the IRIS summaries of these studies, which are reproduced below, there is limited evidence for benzyl chloride-induced skin carcinomas in mice following dermal exposure and injection site sarcomas in rats following subcutaneous injection.

Fukuda et al. (1981) conducted two skin-painting studies on specific-pathogen-free ICR mice, using benzyl chloride dissolved in benzene. Benzene-only controls were included for vehicle comparison. In the first study, no tumors were observed in 11 mice treated with 10 µL benzyl chloride 3 times/week for 4 weeks, followed by 2 times/week until termination at 40 weeks. In the second study, 2.3 µL benzyl chloride was diluted to a final volume of 25 µL with benzene and applied to the skin of 7-week-old mice 2 times/week for 50 weeks. There were 2/20

control animals that developed lung adenomas, while 5/20 treated mice developed tumors, including 2 lung adenomas and 3 skin carcinomas. Two of the skin carcinomas metastasized to the primary lymphatic organs, liver or kidneys. Although these tumor incidences are not statistically significantly greater than controls, the authors considered benzyl chloride to be a weak carcinogen when applied topically. The short duration of the studies limited their sensitivity.

Ashby et al. (1982) topically treated groups of 20 Swiss mice with 100 μg benzyl chloride in toluene twice weekly. After 7.5 months, none of the treated mice had skin tumors compared with 18/20 of the positive controls treated with benzo[a]pyrene.

Coombs (1982a) applied 1.0 mg benzyl chloride in toluene to the backs of 40 T.O. (Swiss- Webster derived Theiler's Original) mice, followed by twice weekly treatments of croton oil in toluene for 10 months. While 8/19 positive controls treated with 0.4 mg benzo[a]pyrene developed skin tumors, none (0/37) of the benzyl chloride-treated mice did. In a second initiation-promotion test, Coombs (1982b) topically applied 10, 100 or 1000 μg benzyl chloride in acetone, followed by twice weekly applications of the promotor 12-O-tetra-'3-decanoyl-phorbol-'3-acetate. At the end of 11 weeks, all of the positive controls treated with 7,12-dimethylbenz[a]anthracene had skin tumors, whereas at 6 months (approximately 12 weeks later), only 20% of the mice treated with benzyl chloride showed similar changes.

Druckrey et al. (1970) administered benzyl chloride in peanut oil via weekly subcutaneous injection to BD-strain rats for 51 weeks. Local sarcomas were produced in 3/14 rats given 40 mg/kg/week and in 6/8 rats given 80 mg/kg/week. The average induction time was 500 days and metastases to the lung occurred in the high-dose group only.

Groups of 20 strain A/H mice were injected intraperitoneally over a 24-week period with benzyl chloride in tricaprylin (total doses of 4.7, 11.8 or 15.8 mmol/kg). No differences in pulmonary adenoma formation between treated and vehicle control mice were observed (Poirier et al., 1975).

Genotoxicity – Genotoxicity studies of benzyl chloride were evaluated by EPA in the 1989 carcinogenicity assessment of benzyl chloride on IRIS (U.S. EPA, 2007) and more recently by IARC (1999). These evaluations indicate that benzyl chloride induced DNA damage and mutagenicity in bacteria; sister chromatid exchanges, chromosomal aberrations, mutations, and DNA strand breaks in cultured rodent cells; and DNA breaks, but not chromosomal aberrations, in cultured human cells. Conflicting results were reported for induction of sister chromatid exchanges in cultured human cells and negative results were reported for induction of micronuclei and sperm head abnormalities in mice *in vivo.*

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR BENZYL CHLORIDE

Subchronic p-RfD

Information relevant to provisional subchronic RfD derivation is available from subchronic toxicity studies in rats and mice (Bunner and Creasia, 1982; Lijinsky, 1986; Reuber, 1979) and developmental toxicity studies in rats and rabbits (Monsanto Co., 1977a; Skowronski and Abdel-Rahman, 1986).

In the subchronic study in rats, doses ranging from 15-250 mg/kg-day were administered by gavage 3 days/week for up to 27 weeks (females) or 37 weeks (males) (Bunner and Creasia, 1982; Lijinsky, 1986; Reuber, 1979). Heart lesions (hyperplastic changes and myocardial necrosis) occurring in males at $\geq$15 mg/kg-day were established as the basis for the LOAEL. Although quantitative incidence was not reported, the fact that most male rats were affected at the lowest dose adequately defines a subchronic LOAEL of 15 mg/kg-day for cardiac lesions. A NOAEL was not established.

The observed cardiac effects are rare in rats and were not observed in the chronic study using the same strain of rats (Lijinsky, 1986), which suggests that the effects may not be a result of benzyl chloride exposure. There is no explanation of the discrepancy in the chronic study report. There is no evidence of microbial involvement in the elicitation of these effects and no reference to a specific pathogenic origin for these effects could be found in the literature. There was an apparent dose-related increase in the incidence and severity of the lesions, however. In addition, similar effects have been induced in rats treated with isoproterenol (Pearl and Balazs, 1967), although there is no substantive structural similarity between benzyl chloride and isoproterenol. Therefore, other than the absence of these effects in the chronic study, there is no reason to reject them as the basis for the pRfD.

In the subchronic study in mice, doses ranging from 6.3-100 mg/kg-day were administered by gavage 3 days/week for up to 26 weeks (Lijinsky, 1986). Liver hyperplasia was the only reported effect, but effect levels and incidences were not specified, precluding identification of a NOAEL or LOAEL in the mice.

The developmental toxicity study in rabbits (Monsanto Co., 1977a) administered benzyl chloride by capsule on GD 6-18 and identified a NOAEL of 30 mg/kg-day, but no LOAEL, for maternal and developmental toxicity. The developmental study in rats (Skowronski and Abdel-Rahman, 1986) used gavage administration on GD 6-15 and identified a NOAEL of 100 mg/kg-day, but no LOAEL, for maternal toxicity and a NOAEL of 50 mg/kg-day and a LOAEL of 100 mg/kg-day for developmental toxicity (minor fetotoxicity manifested as slightly reduced crown-rump length). Although no maternal toxicity was observed at 100 mg/kg-day, this NOAEL is in the range of doses that increased mortality in the subchronic rat study and is considerably higher than the 15 mg/kg-day subchronic LOAEL for cardiac lesions.

The 15 mg/kg-day LOAEL for cardiac lesions in male rats (Bunner and Creasia, 1982) was used to derive the subchronic p-RfD; use of benchmark dose analysis was precluded by

unreported quantitative incidence data. The LOAEL was first adjusted for intermittent exposure, as follows:

$$\begin{aligned} \text{Adjusted LOAEL } (LOAEL_{ADJ}) &= \text{LOAEL x (days/week)} \\ &= \text{15 mg/kg-day x (3 days/7 days)} \\ &= \text{6.4 mg/kg-day} \end{aligned}$$

The $LOAEL_{ADJ}$ of 6.4 mg/kg-day was divided by a composite uncertainty factor of 3000 to derive a **subchronic p-RfD of 2E-03 mg/kg-day**, as follows:

$$\begin{aligned} \text{Subchronic p-RfD} &= LOAEL_{ADJ} \div UF \\ &= \text{6.4 mg/kg-day} \div 3000 \\ &= \text{0.002 or 2E-3 mg/kg-day} \end{aligned}$$

The uncertainty factor (UF) of 3000 was composed of the following:

- A full default UF of 10 was applied for interspecies extrapolation to account for potential pharmacodynamic and pharmacokinetic differences between rats and humans.
- A full default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of quantitative information or information on the variability of response in humans.
- A full default UF of 10 was applied for use of a LOAEL. A NOAEL was not identified.
- A partial UF of 3 ($10^{0.5}$) was included for database insufficiencies due to the limited supporting data available and lack of a multi-generation reproduction study.

Confidence in the key subchronic toxicity study in rats is low. This study used a wide range of dose levels and included comprehensive histological examinations, but hematology, clinical chemistry and urinalysis were not evaluated. This study is further limited by incomplete reporting of nonneoplastic lesions, particularly a lack of quantitative incidence data for the critical effect (cardiac lesions). In addition, cardiac lesions are rare in rats and were not seen in the chronic study (Lijinsky, 1986). Confidence in the database is low. A subchronic study is available in a second species (mouse), but the design is the same as the rat study and reporting inadequacies preclude identification of effect levels. Adequate developmental toxicity studies are available in two species (rats and rabbits), but reproductive toxicity has not been evaluated. Low confidence in the subchronic p-RfD results.

Chronic p-RfD

Limited information on the chronic oral toxicity of benzyl chloride is available from carcinogenicity studies in which rats and mice were treated by gavage 3 days/week for 104 weeks (Lijinsky, 1986). In the rat study, it was reported that exposure to 15 or 30 mg/kg-day did not cause any significantly increased incidences of non-neoplastic lesions, implying that 30 mg/kg-day was a chronic NOAEL. This NOAEL is equivocal and not useful for RfD derivation

because additional information on non-neoplastic effects, including incidence data and a discussion of results, was lacking. Thus, the chronic exposure study did not provide evidence of the heart and stomach lesions observed in the subchronic rat study (Bunner and Creasia, 1982; Lijinsky, 1986; Reuber, 1979) for which there was no explanation (see previous section). The chronic study in mice used dose levels of 50 and 100 mg/kg-day and found significantly increased incidences of tumors, particularly forestomach carcinomas and papillomas, at 100 mg/kg-day. Nonneoplastic lesions in mice were limited to stomach epithelial hyperplasia in animals without stomach tumors, but unreported effect levels and incidence data preclude identification of a NOAEL or LOAEL. Although it is possible that 50 mg/kg-day was a chronic LOAEL for stomach hyperplasia in mice, this dose is higher than the subchronic LOAELs for stomach and heart lesions in rats (30 and 15 mg/kg-day, respectively).

Because reporting limitations preclude identification of an unequivocal NOAEL or LOAEL for chronic toxicity, the subchronic p-RfD provided the best basis for deriving a chronic p-RfD. An uncertainty factor of 1 was applied to the subchronic p-RfD to extrapolate from subchronic to chronic duration because the apparent lack of cardiac lesions in the chronic rat study suggests that a longer exposure duration may not have an effect on the LOAEL. The **chronic p-RfD of 2E-3 mg/kg-day** is derived as follows:

Chronic p-RfD	=	Subchronic p-RfD ÷ UF
	=	0.002 mg/kg-day ÷ 1
	=	0.002 or 2E-3 mg/kg-day

Confidence in the subchronic toxicity study used to derive the chronic p-RfD is low, as discussed in the subchronic p-RfD derivation. The database includes chronic toxicity studies in two species and adequate developmental toxicity studies in two species. Confidence in the database is low because the chronic studies, primarily designed as carcinogenicity bioassays, provided incomplete reporting of noncancer endpoints. Reproductive toxicity studies have not been conducted. The chronic study (Lijinsky, 1986), however, did conduct histopathology on all major organs following NCI study protocol. Although negative findings were not explicit, it seems highly unlikely that cardiac effects so evident in the subchronic study could have been overlooked in the chronic study. Low confidence in the chronic p-RfD results.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR BENZYL CHLORIDE

Subchronic p-RfC

The subchronic inhalation toxicity of benzyl chloride has been tested in intermittent exposure (6 hours/day, 5 days/week) studies of rats, guinea pigs and hamsters exposed to 12, 35 or 102 ppm vapor for 5 weeks (Monsanto Co., 1983) and rats and guinea pigs exposed to 1, 12 or 28.6 ppm vapor for 27 weeks (Monsanto Co., 1984). Endpoints in the 5-week studies were limited to clinical signs, mortality, body weight and gross pathology in all species, and lung histology in a small number of guinea pigs (2/sex/dose). The 27-week studies additionally included comprehensive histology examinations (including nasal turbinates, trachea and lung)

and hematology, clinical chemistry and urinalysis evaluations in both species. Short-term studies of respiratory tract histopathology were conducted in mice exposed to 22 or 46 ppm vapor for 6 hours/day, 5 days/week for 4-14 days (Zissu, 1995) and rats exposed to 8.7 or 38 ppm (as an aerosol) for 4 weeks (hours/day and days/week of exposure not reported; aerosol not characterized) (Rohm and Haas Co., 1988). The study results and adjusted and human-equivalent NOAELs and LOAELs are shown in Table 3.

Table 3. Benzyl Chloride Inhalation Toxicity Studies in Rodents

Species (study)	Exposure duration	NOAEL [a] LOAEL	$NOAEL_{ADJ}$ [b] $LOAEL_{ADJ}$	RGDR [c] (region)	$NOAEL_{HEC}$ [d] $LOAEL_{HEC}$
Mouse	2 weeks	114 (22)	20.4	0.97	19.7
(Zissu, 1995)	(maximum)	238 (46)	42.5	(ET)	41.0
Rat	2 weeks	none		2.59	
(Monsanto 1977b)		75 (14.4)	13.4	(PU)	34.7
Rat	5 weeks	180 (35)	32.1	2.59	83.0
(Monsanto 1983)		530 (102)	94.6	(PU)	245
Guinea pig	5 weeks	60 (12)	10.7	0.335	3.58
(Monsanto 1983)		180 (35)	32.1	(PU)	10.8
Hamster	5 weeks	180 (35)	32.1	0.339	10.9
(Monsanto 1983)		530 (102)	94.6	(PU)	32.1
Rat	27 weeks	148 (28.6)	26.4	2.59	68.4
(Monsanto 1984)		None		(PU)	
Guinea pig	27 weeks	148 (28.6)	26.4	0.525	13.9
(Monsanto 1984)		None		(PU)	

[a] nominal (unadjusted exposure) in mg/m^3 (ppm)
[b] adjusted for exposure schedule (mg/m^3)
[c] regional gas dose ratio for region indicated (based on default body weights)
[d] $N(L)OAEL_{ADJ}$ x RGDR(mg/m^3)

No adverse effects occurred at any exposure concentration tested in the 27-week studies yielding a NOAEL of 28.6 ppm in guinea pigs and rats. Effects on the respiratory tract and decreased body weight occurred at higher concentrations in the 5-week studies, which identified a NOAEL of 12 ppm and LOAEL of 35 ppm in guinea pigs based on gross and microscopic lung lesions, a NOAEL of 35 ppm and LOAEL of 102 ppm in rats based on respiratory clinical signs (sneezing and congested breathing) and decreased body weight gain, and a NOAEL of 35 ppm and LOAEL of 102 ppm in hamsters based on signs of nasal irritation (sneezing), eye irritation and decreased body weight gain. No clinical signs or other effects were observed in the guinea pigs exposed to 35 ppm (the LOAEL for lung lesions); clinical signs of respiratory tract and eye irritation (sneezing, labored breathing, nose/mouth wetness, eye irritation and lacrimation) occurred at 102 ppm, the same concentration causing similar clinical signs in rats and hamsters. However, no gross lung lesions (lung histology not evaluated) were observed in rats or hamsters, even at the concentration causing clinical signs (102 ppm). Results of the 5-week studies indicate that the respiratory tract was a target in all three species, with the guinea pig more sensitive to benzyl chloride-induced effects than rats and hamsters; lung lesions were identified as the critical effect in guinea pigs.

As indicated above, respiratory effects in the 5-week studies included clinical signs of nasal irritation in guinea pigs, rats and hamsters at 102 ppm, but not at 35 ppm, the LOAEL for gross lung lesions in guinea pigs. However, clinical signs may not be as sensitive as histopathological changes for defining the NOAEL and LOAEL for benzyl chloride effects to the upper respiratory tract. Data from the 5-week studies do not provide clarification on this issue, since nasal histopathology was not evaluated. The 27-week study (Monsanto Co., 1984) identified a NOAEL of 28.6 ppm for both clinical signs and nasal (and lung) histopathology in guinea pigs and rats, but there is some uncertainty regarding the lack of nasal lesions, because it is not known if the nasal tissue sectioning practices are adequate by current standards and nasal histology was not examined in lower exposure groups ($\leq$12 ppm). Short-term studies (Rohm and Haas Co., 1988; Zissu, 1995) found nasal lesions in rats and mice at concentrations similar to the 5-week LOAEL for gross lung pathology in guinea pigs (35 ppm). Exposure to 38 ppm (as an aerosol) for 4 weeks caused mucosal lesions (hyperplasia and non-keratizing squamous metaplasia) in the anterior nasal turbinates in rats (Rohm and Haas Co., 1988); however, comparison of LOAEL values from the 4- and 5-week studies is compromised by unreported daily exposure duration, use of an uncharacterized aerosol, and lack of lung pathology evaluation in the 4-week study. In mice, exposure to 46 ppm for 6 hours/day, 5 days/week for 4-14 days caused nasal lesions graded as severe or very severe, in the anterior respiratory epithelium (rhinitis, metaplasia, necrosis) and olfactory epithelium in the dorsal meatus (extensive loss of sensory epithelium with damage to sustentacular cells), but no histopathology in the trachea or lungs (Zissu, 1995). No nasal lesions were observed in the mice at 17 ppm, although nasal irritation apparently occurred because this level was the acute RD_{50} [i.e., concentration at which respiratory rate in Swiss mice is decreased by 50% during a 15-minute exposure due to sensory irritation (trigeminal nerve stimulation) in the nasal mucosa]. However, 17 ppm was classified as a NOAEL for nasal irritation because there was no upper or lower respiratory tract histopathology at this concentration and the relevance of the mouse RD_{50} test for evaluating respiratory tract irritation in humans is unclear (Bos et al., 1991, 2002). The short-term studies indicate that nasal effects are an additional sensitive respiratory endpoint for benzyl chloride, but do not provide a suitable basis for RfC derivation because adverse nasal effects (histopathology) did not occur in mice or rats at concentrations below the 5-week NOAEL of 35 ppm for lung lesions in guinea pigs.

Benchmark Concentration (BMC) modeling was performed for the two endpoints defining the LOAEL in the Monsanto Co. (1983) 5-week inhalation study on guinea pigs. The two endpoints were pulmonary edema and pulmonary hemorrhage (see Table 2). All the dichotomous models in BMDS, version 1.4.1 (U.S. EPA, 2008), were fit to the nominal exposure concentrations (in mg/m^3) for each endpoint for estimation of a $BMCL_{10}$. None of the models provided an adequate fit to the pulmonary hemorrhage data. The model fits to the pulmonary edema data are shown in Table 4. Several of the models fit adequately to the pulmonary edema endpoint. Unconstrained model fits for the two-parameter models resulted in slope or power parameters less than one, with $BMCL_{10}$ estimates several orders of magnitude below the BMD. The log-logistic model provides the best fit on the basis of the lowest AIC; it also provides the lowest $BMCL_{10}$. The log-logistic $BMCL_{10}$ of 19.58 mg/m^3 corresponds to a $BMCL_{HEC}$ of 1.17 mg/m^3 after adusting for exposure regimen (6 hours per day, 5 days per week) and multiplying by the RGDR of 0.335.

Table 4. Benchmark Concentration modeling results for pulmonary edema endpoint in guinea pigs exposed to benzyl chloride by inhalation for 5 weeks

Model	p-value	AIC	BMC_{10}[a]	$BMCL_{10}$
log-logistic (constrained)[b]	0.63	37.93	38.12	19.58
multi-stage[c]	0.40	38.93	54.06	33.75
gamma (constrained)[d]	0.40	38.93	54.06	33.75
log-probit (constrained)	0.21	40.25	79.87	52.54
log-logistic (unconstrained)	0.45	39.84	28.32	4.1×10^{-5}

[a] mg/m^3
[b] for all constrained models, slope or power parameters hit lower bound of 1
[c] 2nd order model fit; only 1st order parameter was significant
[d] constrained gamma (and Weibull) models reduce to 1st-order multistage and provide identical fits
Source: Monsanto Co., 1983

The $BMCL_{10}$ of 19.58 mg/m^3 for lung lesions in guinea pigs in the 5-week study (Monsanto Co., 1983) was used to calculate a subchronic p-RfC. The BMCL was first duration adjusted for intermittent exposure (6 hours/day, 5 days/week), as follows:

$BMCL_{ADJ}$ = BMCL x (hours/day) x (days/week)
= 19.58 mg/m^3 x (6 hours/24hours) x (5 days/7 days)
= 3.50 mg/m^3

Benzyl chloride exhibited its toxic effects in the lungs and, because of its reactivity, is treated as a Category 1 gas for purposes of calculating the p-RfC (U.S. EPA, 1994b). Benzyl chloride's reactivity is demonstrated by the nature of the respiratory effects previously described and by its rapid hydrolysis in water (U.S. EPA, 1986); no significant accumulation of benzyl chloride in blood is expected that would lower the rate of absorption over time. The human equivalent concentration (HEC) for a Category 1 gas with effects in the lungs is calculated by multiplying the duration-adjusted BMCL by the regional gas dose ratio in the pulmonary region ($RGDR_{PU}$) (U.S. EPA, 1994b). Using values for guinea pigs and humans, an $RGDR_{PU}$ of 0.335 was determined using the following equation:

$$RGDR_{PU} = \frac{\left(Dose_{PU}\right)_A}{\left(Dose_{PU}\right)_H} = \frac{\left(\frac{\dot{Q}_{alv}}{SA_{PU}}\right)_A}{\left(\frac{\dot{Q}_{alv}}{SA_{PU}}\right)_H} \frac{\left(e^{-\frac{SA_{TB}}{\dot{V}_E}}\right)_A}{\left(e^{-\frac{SA_{TB}}{\dot{V}_E}}\right)_H} \frac{\left(e^{-\frac{SA_{ET}}{\dot{V}_E}}\right)_A}{\left(e^{-\frac{SA_{ET}}{\dot{V}_E}}\right)_H}$$

where:

A and H	=	subscripts for animal (guinea pig) and human values
$Dose_{PU}$	=	Dose in pulmonary region
Q_{alv}	=	Alveolar ventilation rates, in cm^3/min
		131 cm^3/min for guinea pig
		9246 cm^3/min for human

SA_{PU}	=	Surface area of pulmonary region in m^2 0.9 m^2 for guinea pig 54 m^2 for human
SA_{TB}	=	Surface area of tracheobronchial region in cm^2 200 cm^2 for guinea pig 3200 cm^2 for human
SA_{ET}	=	Surface area of extrathoracic region in cm^2 30 cm^2 for guinea pig 200 cm^2 for human
V_E	=	Minute volume in cm^3/min 195 cm^3/min for guinea pig 13,800 cm^3/min for human

The alveolar ventilation rates were calculated as 67% of the minute volumes according to U.S. EPA (1988). The regional surface areas for guinea pigs and humans and the minute volume for humans were taken from U.S. EPA (1994b). The minute volume for guinea pigs was calculated using the time-weighted average body weight in the Monsanto Co. (1984) study, 0.425 kg and the intercept and coefficient values provided in Table 4-6 of U.S. EPA (1994b) for the algorithm:

$$\ln (V_E) = b_0 + b_1 [\ln(BW)]$$
$$\ln (V_E) = -1.191 + 0.516 [\ln(0.425)]$$
$$V_E = 195 \text{ cm}^3\text{/min}$$

The $BMCL_{HEC}$ is then calculated from the $BMCL_{ADJ}$ and $RGDR_{PU}$, as follows:

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR_{PU}$$
$$= 3.50 \text{ mg/m}^3 \times 0.335$$
$$= 1.17 \text{ mg/m}^3$$

A **subchronic p-RfC of 0.004 mg/m^3** was derived by dividing the $BMCL_{HEC}$ of 1.17 mg/m^3 by a composite uncertainty factor (UF) of 300, as follows:

$$\text{Subchronic p-RfC} = NOAEL_{HEC} \div UF$$
$$= 1.17 \text{ mg/m}^3 \div 300$$
$$= 0.004 \text{ or } 4E\text{-}3 \text{ mg/m}^3$$

The composite uncertainty factor of 300 is composed of the following:

- A full default 10-fold UF for intraspecies differences is used to account for potentially susceptible individuals in the absence of information on the variability of response in humans. Individuals with pre-existing respiratory disorders, such as asthmas or emphysema may be more susceptible to inhaled benzyl chloride.

- A partial UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between guinea pigs and humans. Converting the rat data to human equivalent concentrations by the dosimetric equations accounts for pharmacokinetic differences between guinea pigs and humans; thus, it was not necessary to use the default UF of 10 for interspecies extrapolation.
- A full default UF of 10 is included for database insufficiencies. Supporting systemic toxicity data are limited and the database lacks reproductive and developmental toxicity studies by the inhalation route.

Confidence in the key study is low. The 5-week study in guinea pigs was well-designed as a short-term range-finding study, but used few animals and did not conduct histopathological examinations. In addition, the pulmonary effects were not observed in the longer-term 27-week study. The 27-week study in guinea pigs was well-designed, used adequate numbers of animals, a wide variety of endpoints (including comprehensive histopathological examinations) and appropriate controls. However, histopathological examinations were limited to 10 animals in the control and high-dose groups and possibly insufficient for nasal tissues, and the (equivocal) LOAEL was much higher than the short-term LOAEL in the 5-week study. Confidence in the database is low-to-medium because a companion 27-week study in a second species (rat) has the same limitations as the 27-week guinea pig study and 5-week studies in rats and hamsters lack histopathological evaluations. Subchronic studies with adequate nasal histopathology assessments are needed to corroborate the sensitive nasal effects observed in short-term studies in rats and mice, and reproductive and developmental toxicity studies have not been conducted (although developmental toxicity has been tested following oral exposure). Low confidence in the subchronic p-RfC results.

Chronic p-RfC

No chronic inhalation toxicity studies of benzyl chloride have been conducted, indicating that the subchronic $BMCL_{HEC}$ provides the best basis for deriving a chronic p-RfC. An additional UF of 3 ($10^{0.5}$) is applied to extrapolate from subchronic to chronic exposure, making the composite UF equal to 1000. A partial UF is used for duration extrapolation because the data suggest that exposure duration may not be a main determinant for lung effects and the 27-week duration of the supporting guinea pig study is closer to chronic exposure than a standard 90-day subchronic study. Application of the composite UF yields a **chronic p-RfC of 0.001 mg/m^3**, as follows:

$$\begin{aligned} \text{Chronic p-RfC} &= NOAEL_{HEC} \div UF \\ &= 1.17\ mg/m^3 \div 1000 \\ &= 0.001 \text{ or } 1E\text{-}3\ mg/m^3 \end{aligned}$$

Confidence in the 5-week study used to derive the subchronic p-RfC is medium, as discussed for subchronic p-RfC derivation. Confidence in the database is low due to the lack of chronic inhalation data and for the reasons discussed for the subchronic p-RfC, including uncertainty in the adequacy of nasal toxicity assessment and lack of reproductive and developmental toxicity data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR BENZYL CHLORIDE

No oral cancer values were developed since an OSF exists on IRIS (U.S. EPA, 2007).

No inhalation values were developed because of a lack of data.

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APPENDIX A. Benchmark Concentration Modeling for Pulmonary Edema in Guinea Pigs Exposed to Benzyl Chloride by Inhalation for 5 Weeks (Monsanto Co., 1983)

Lung edema
5 week Guinea pig inhalation study (Monsanto, 1983)

```
================================================================================
        Logistic Model. (Version: 2.9; Date: 02/20/2007)
        Input Data File: C:\BMDS\DATA\BENZYL_CHORIDE_RFD.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\BENZYL_CHORIDE_RFD.plt
                                        Thu Jan 24 14:18:19 2008
================================================================================

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

  The form of the probability function is:

  P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

  Dependent variable = edema
  Independent variable = d
  Slope parameter is restricted as slope >= 1

  Total number of observations = 4
  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

  User has chosen the log transformed model

             Default Initial Parameter Values
               background =           0
                intercept =     -5.97847
                    slope =      1.01144

       Asymptotic Correlation Matrix of Parameter Estimates

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

         intercept

intercept          1
```

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-5.83799	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-17.1138	4			
Fitted model	-17.9641	1	1.70074	3	0.6368
Reduced model	-23.5268	1	12.826	3	0.005029

AIC: 37.9283

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
60.0000	0.1489	1.489	1	10	-0.434
180.0000	0.3441	3.441	5	10	1.038
530.0000	0.6070	6.070	5	10	-0.693

Chi^2 = 1.75 d.f. = 3 P-value = 0.6269

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 38.121

BMDL = 19.5754