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Provisional Peer-Reviewed Toxicity Values for

Boron Trichloride
(CASRN 10294-34-5)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR BORON TRICHLORIDE (CASRN 10294-34-5)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Boron trichloride gases have been used as soldering fluxes for alloys of aluminum, iron, zinc, tungsten, and Monel®; in the plasma etching of aluminum alloys, tungsten, and tungsten silicide; to remove nitrides, carbides, and oxides in the refining of aluminum, magnesium, zinc, and copper alloys; to treat the melt in the casting of aluminum; as a source of boron in high energy fuels and rocket propellants; to douse fires in heat treating ovens that contain magnesium products; as reagents in the synthesis of drug candidates for a range of diseases; and in the fiber industry as raw materials needed to produce pyrolytic boron nitride and boron fiber, components of high-tech composite structures (ATSDR, 2007). Figure 1 shows the chemical structure of boron trichloride. Table 1 presents the physicochemical properties of boron trichloride.

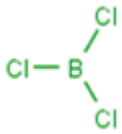

Figure 1. Chemical Structure of Boron Trichloride

Table 1. Physicochemical Properties of Boron Trichloride

Property (unit)	Value	Reference
CASRN	10294-34-5	HSDB (2011a)
Molecular formula	BCl_3	
Molecular weight	117.17 g/mol	
Physical state/Appearance	Colorless fuming liquid at low temperatures	
Odor	Pungent, suffocating odor	
Boiling Point (ºC)	12.5	
Melting point (ºC)	−107	
Vapor density (g/cm^3)v	4.03 (Air = 1)	
Vapor pressure (kPa at 27ºC)	166	
Water solubility	Hydrolyzes upon contact with water into $H_3B\ 0_3$ and HCl	
Other solubilities	Decomposes in alcohol to $H_3B\ 0_3$ and HCl	ATSDR (2007)
Flash point	No data	
Flammability in air	Nonflammable	
Dissociation constant pKa	No data	
Density (g/cm^3)	1.3728 at 0ºC	
Partition coefficient (Log Kow)	No data	
Synonyms	Trichloroborane, trichloroboron	

No RfD, RfC, or cancer assessment for boron trichloride is included in the IRIS database (U.S. EPA, 2011). However, there is an IRIS Toxicological Review document for boron and compounds (CASRN 7440-42-8; U.S. EPA, 2004) that derives a RfD of 0.2 mg/kg-day, based on dietary gestational exposure to boric acid (Price et al., 1996a; Heindel et al., 1992). IRIS determined that the data were inadequate to support derivation of a RfC or a cancer assessment for boron and compounds. IRIS also reports a RfC of 0.02 mg/m^3 for inhalation exposure to hydrogen chloride, a hydrolysis product of boron trichloride. Boron trichloride is not on the Drinking Water Standards and Health Advisories List, but there is a lifetime Health Advisory (HA) for boron (U.S. EPA, 2009) that is based upon the IRIS assessment.

No RfDs or RfCs for boron trichloride are reported in the Health Effects Assessment Summary Tables (HEAST), but there are subchronic and chronic RfCs for elemental boron, based on respiratory tract irritation in humans (U.S. EPA, 1997). The HEAST also list a subchronic RfC and a chronic RfC for boron trifluoride (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not contain any documents for boron trichloride but lists a Health Effects Assessment (U.S. EPA, 1987) and a Health and Environmental Effects Document (U.S. EPA, 1991) for boron and compounds.

The toxicity of boron trichloride has not been reviewed by the ATSDR (2011). However, ATSDR has reviewed the toxicity of boron in its *Toxicological Profile for Boron* (ATSDR, 2007), which derives an inhalation acute minimal risk level (MRL) of 0.01 mg/m^3 for boron and an oral MRL of 0.2 mg/kg-day for both acute and intermediate duration exposures to boron. The World Health Organization (WHO, 2011) has not set guidelines for boron trichloride exposure. However, it set a provisional guideline of 0.5 mg/L for boron in drinking water, based on a tolerable daily intake (TDI) of 0.16 mg/kg-day (WHO, 2003). CalEPA (2008) has not derived toxicity values for boron trichloride or boron.

No occupational exposure limits for boron trichloride have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute for Occupational Safety and Health (NIOSH, 2005), or the Occupational Safety and Health Administration (OSHA, 2011). However, NIOSH (2005) and OSHA (2011) have set occupational recommended and permissible exposure limits, respectively, for boron trifluoride, boron tribromide, and boron oxide. ACGIH (2001a,b,c, 2005, 2011) also derived threshold limit values (TLV) for occupational exposures to boron trifluoride (TLV-Ceiling = 2.8 mg/m^3), boron tribromide (TLV-Ceiling = 10 mg/m^3), boron oxide (TLV-TWA = 10 mg/m^3), and inorganic borates (TLV-TWA = 2 mg/m^3 as inhalable particulate).

The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of boron trichloride, and the compound is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of the carcinogenic potential of boron trichloride.

The only toxicity values proposed were draft acute exposure guideline levels (AEGLs) for inhaled boron trichloride (U.S. EPA, 2000), including the following for 8-hour exposures, with key studies listed parenthetically:

- AEGL-1 (nondisabling): 0.6 ppm (2.9 mg/m^3) based on the no-effect-level of hydrogen chloride (HCl) in exercising human asthmatics (Stevens et al., 1992);

- AEGL-2 (disabling): 0.9 ppm (4.3 mg/m^3) based on studies in mice and rats with HCl (Barrow et al., 1977; Stavert et al., 1991);
- AEGL-3 (lethal) for an 8-hour exposure of 3.5 ppm (17 mg/m^3) based on a 1-hour LC_{50} for boron trichloride in male rats (Vernot et al., 1977).

HCl was used as the basis for the proposed AEGL-1 and AEGL-2 because boron trichloride undergoes rapid hydrolysis to form hydrochloric acid, boric acid and heat in moist air (U.S. EPA, 2000; ATSDR, 2007).

Boron trichloride acute inhalation toxicity is most likely from the irritant effects of its hydrolysis product, hydrochloric acid (U.S. EPA, 2000). Inhalation of boron trichloride results in edema and irritation of the upper respiratory tract (Braker and Mossman, 1980). Boron trichloride has not been found to occur in water because it hydrolyzes to boric acid and HCl in aqueous media (ATSDR, 2007). Boric acid acts as an electron acceptor, accepting a hydroxide ion from water to form boron hydroxide (ATSDR, 2007).

Literature searches were conducted on sources published from 1900 through April 4, 2011 for studies relevant to derivation of provisional toxicity values for boron trichloride, CASRN 10294-34-5. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following sources outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, EPA IRIS, HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Boron is a nonmetal element that always is found in nature covalently bonded to oxygen as some form of borate, such as boric acid or tetraborate (ATSDR, 2007; U.S. EPA, 2004); it never is found as the free element (HSDB, 2011b). The boron-oxygen bonds are very strong and will not be broken except under extreme laboratory conditions. Inorganic borate compounds in the body are present as boric acid. Boric acid is the only boron compound identified in urine following boron ingestion and has repeatedly been found to account for >90% of the ingested boron dose (WHO, 1998).

Boron trichloride hydrolyzes easily in water, moist air, or ethanol to boric acid and HCl (ATSDR, 2007) (see Table 1), as represented by the following equation:[1]

$$\mathbf{BCl_3 + 3\ H_2O \rightarrow H_3BO_3 + 3\ HCl}$$

With the exception of acute inhalation lethality studies, there are no toxicological data on boron trichloride. Therefore, available literature is reviewed for boron, predominantly as boric acid, and for HCl, to determine which component might drive the oral or inhalation toxicity of BCl_3. Available data on hydrolysis, reactivity, and toxicokinetics support this approach (U.S. EPA, 2000; ATSDR, 2007).

Tables 2 and 3 present potentially relevant toxicological data available for the hydrolysis products of boron trichloride: boric acid and hydrogen chloride, respectively. Doses of boric acid have been provided in mg-B/kg-day for all studies reported in Table 2.

[1]Assuming that hydrolysis is complete or near complete.

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
Human								
			1. Oral (mg/kg-d)[a]					
Acute	2 infants (gender not reported), case report, duration not reported	30.4−94.7	Diarrhea, erythema, vomiting, face and skin rash	None	Not run	30.4	Baker et al. (1986) (Boron as boric acid)	
	7 infants (gender not reported), case report, duration not reported	Not reported	Seizures	None	Not run	None	O'Sullivan and Taylor (1983) (Honey-borax)	
	Number and gender not reported, case report, 15 d	2.5−24.8	Indigestion, dermatitis, alopecia, anorexia	2.5	Not run	3.68	Culver and Hubbard (1996) (Boron as boron compounds, unspecified)	
Subchronic	Number and gender not reported, case report, duration not reported	25−35	Nausea, vomiting, skin flush	2.5[b]	Not run	25	Culver and Hubbard (1996) (Boron as boron compounds, unspecified)	
Chronic	"Nearly 1000" male workers; epidemiology	0.02, 0.06 (control groups), 0.45, 1.8	Reduced sperm Y:X ratio	None	Not run	0.45	Scialli et al. (2010)	
Developmental	None							
Reproductive	None							
Carcinogenic	None							

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
2. Inhalation (mg/m^3)[a]								
Subchronic	None							
Chronic	Number and gender not reported, occupational, duration not reported	Not reported	Dermatitis, nasal irritation, nose bleeds, cough, shortness of breath	None	Not run	None	Birmingham and Key (1963) (Boron as boron compounds, unspecified) Concomitant exposure to other compounds	
	82, male, occupational, at least 1 yr	Not reported	Respiratory symptoms (focused expiratory volume)	None	Not run	None	Ury (1966) (Sodium borate dust)	
	629, 96% males, occupational, ≥5 yr	1.1−14.6	Symptoms of respiratory irritation	None	Not run	1.1	Garabrant et al. (1984, 1985) (Boric acid or boron oxide)	
	113, 96% males, occupational, ≥5 yr	4.1 (Range 1.2−8.5)	Eye irritation, dryness of mouth, nose, or throat, sore throat, cough during work shift	None	Not run	4.1	Garabrant et al. (1984) (Boric acid or boron oxide)	
	336, gender not reported, occupational, ≥5 yr	1.1−14.6	No exposure-related change in pulmonary function. Nasal, eye and throat irritation; cough and breathlessness.	None	Not run	~5	Wegman et al. (1994) (Boric acid or boron oxide)	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
Developmental	None							
Reproductive	28, male, occupational, ≥10 yr	(Range 22−80)	Low sperm count, reduced sperm motility, elevated fructose content of seminal fluid, decreased sexual function	None	Not run	22	Tarasenko et al. (1972) (Boron as boric acid) Concomitant exposure to other compounds, study limited by poor reporting	
	542, male, occupational, average = 15.8 yr	<0.82 mg/m^3 to 5.05	Standardized birth ratios	None	Not run	5.05	Whorton et al. (1992, 1994a,b) (Boron as sodium borates)	
	68, female, occupational, not reported	Not reported	No change in fertility or offspring gender ratio	None	Not run	None	Whorton et al (1992) (Sodium borates)	
	904, female, occupational, not reported	Not reported	No association with spontaneous abortions	None	Not run	None	Swan et al. (1995) (Boron compounds unspecified) Concomitant exposures to other compounds.	
Carcinogenic	None							

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
Animal								
			1. Oral (mg/kg-d)[a]					
Subchronic	10 male/10 female/group, Sprague-Dawley rat, dietary, 90 d	0, 2.6, 8.8, 26.3, 87.5, 262.5	Mortality at 262.5 mg/kg-d; clinical toxicity; decreased body weight at 87.5 mg/kg-d, and testicular atrophy in one rat at 26.3 mg/kg-d.	8.8	Not run	26.3	Weir and Fisher (1972) (Boron as boric acid)	
	10 male/10 female/group, B6C3F_1 mouse, dietary, 13 wk	M: 0, 34, 70, 141, 281, 563 F: 0, 47, 97, 194, 388, 776	>60% mortality and clinical signs at highest dose; body weight decreased in both sexes; blood effects in both sexes and testicular atrophy/degeneration in males at three highest doses	M: 70 F: 97	Not run	M: 141 F: 194	NTP (1987), Dieter (1994) (Boron as boric acid)	
	5 male/5 female/group, beagle dog, dietary, 90 d	M: 0, 0.33, 3.9, 30.4; F: 0, 0.24, 2.5, 21.8	Testes primary target organ only in high-dose group. Testicular atrophy, tubular degeneration. No effects at lower doses. Some high-dose blood effects in both sexes	M: 3.9 F: 2.5	Not run	M: 30.4 F: 21.8	Weir and Fisher (1972) (Boron as boric acid).	
Chronic	35 male/35 female/group, Sprague-Dawley rat, dietary, 104 wk	0, 5.9, 17.5, 58.5	Effects restricted to highest dose. Clinical signs, decreased body weight, testicular atrophy	17.5	Not run	58.5 (FEL)	Weir and Fisher (1972) (Boron as boric acid)	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
	50 male/50 female/group, $B6C3F_1$ mouse, dietary, 103 wk	0, 48, 96	Increased mortality in low-dose males. Testicular atrophy, interstitial hyperplasia, increase in splenic lymphoid depletion only at highest dose	None	Not run	48 (FEL)	NTP (1987), Dieter (1994) (Boron as boric acid)	
	4 male/4 female/group, beagle dog, dietary, 104 wk Interim sacrifice at 52 wk	0, 1.4, 2.9, 8.8	No effects observed at 52 or 104 wk	8.8	Not run	None	Weir and Fisher (1972) (Boron as boric acid). Highest dose tested is a NOAEL	
	4 male/4 female/group, beagle dog, dietary, 38 wk Interim sacrifice at 26 wk 25-d postdosing recovery.	0, 29.2	Some testicular atrophy and spermatogenic arrest observed at both sacrifice periods. Recovery during 25-d postdosing period	None	Not run	29.2	Weir and Fisher (1972) (Boron as boric acid). Only one dose tested	
Developmental	**29 time-mated females/group Sprague-Dawley rat, dietary, GDs 0−20 or dietary GDs 6−15**	**0, 13.6, 28.5, 57.7 (GDs 0−20) 0, 942 (GDs 6−15)**	**Maternal toxicity in mid- and high-dose group.** Prenatal mortality increased at high-dose. **Decreased fetal weight at all doses.** Skeletal and other malformations or variations at mid- and high-dose	**Maternal: 13.6 Developmental: None**	**Not run Developmental: 10.3[c]**	**Maternal: 28.5 Developmental: 13.6**	**Heindel et al. (1992, 1994) NTP (1990a) (Boron as boric acid).**	**PS[d]**

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
	60 time-mated females/group CD rat, dietary, GDs 0−20 (Phase I)	**0, 3.3, 6.3, 9.6, 13.3, 25**	No maternal toxicity. **Fetal body weights decreased in two highest-dose groups.** Increased skeletal, but not external or visceral, malformations in two highest-dose groups	**Maternal: 25** **Developmental: 9.6**	**Not run** **Developmental: 10.3[c]**	**Maternal: ND** **Developmental: 13.3**	**NTP (1994), Price et al. (1996a) (Boron as boric acid)**	**PS[d]**
	60 female/group CD rat, dietary, GD 0−PND 21 (Phase II)	**0, 3.2, 6.5, 9.7 12.9, 25.3**	Increased mortality in high-dose pups during PNDs 0−4 was within historical control range. No differences in pup weights from PNDs 0−21. **Only skeletal malformation postnatal period time was short rib XIII**	**Maternal: 25.3** **Developmental: 12.9**	**Not run**	**Maternal: ND** **Developmental: 25.3**	**NTP (1994), Price et al. (1996a) (Boron as boric acid)**	**PS**
	28−29 time-mated females/group CD-1 mouse, dietary, GDs 0−17	0, 43.4, 79.0, 175.3	Kidney and liver maternal effects at mid- and high-dose. Fetal body weights decreased at mid- and high-dose. Some increases in resorption rates and fetal skeletal malformations at high-dose	Maternal: 43.4 Developmental: 43.4	Not run	Maternal: 79.0 Developmental: 79.0	Heindel et al. (1992, 1994), NTP (1989) (Boron as boric acid)	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
	30 artificially inseminated females/group New Zealand White rabbit, gavage, GDs 6−19	0, 10.9, 21.9, 43.7	No mortality. At high-dose, vaginal bleeding , reduced live litters, reduced litter size, reduced fetal body weights, and increased visceral malformations in live fetuses/litter. No effects at other doses	Maternal: 21.9 Developmental: 21.9	Not run	Maternal: 43.7 Developmental: 43.7	Heindel et al. (1994) (Boron as boric acid)	
Reproductive	10 male/group Sprague-Dawley rat, drinking water, 30, 60, 90 d	0, 0.042, 0.14, 0.84	No effects on male fertility in breeding studies. No effects on body weight, weights of testis, prostate, seminal vesicles, plasma FSH, plasma LH	0.84	Not run	None	Dixon et al. (1976) (Boron as borax)	
	18 male/group Sprague-Dawley rat, drinking water, 30, 60 d.	0, 25, 50, 100	At mid- and high-dose, decrease in liver, testis, epididymis weights. Dose-related tubular germinal aplasia, reduced fertility at mid- and high-dose	25	Not run	50	Lee et al. (1978); Dixon et al. (1979) (Boron as borax)	
	6 male/group Sprague-Dawley rat, single-dose gavage, evaluation at 2, 14, 28, or 57 d postdosing	0, 350	Increase in abnormal caput and cauda epididymal sperm morphology, decrease in percentage of motile cauda spermatozoa on Day 28. Return to control levels of all sperm parameters in all treated animals by Day 57	None	Not run	None	Linder et al. (1990) (Boron as boric acid.) Time-response study	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
	8 male/group Sprague-Dawley rat, single-dose gavage, evaluation at 14 d postdosing	0, 44, 87, 175, 350	Effects on spermiation, epididymal sperm morphology, and caput sperm reserves at two highest doses	87	Not run	175	Linder et al. (1990) (Boron as boric acid)	
	8 male/group/16 female/group, Sprague-Dawley rat, dietary, through F3 generation	0, 5.9, 17.5, 58.5	At high-dose, no litters produced, no spermatozoa in atrophied testes in males, decrease in ovulation in females. No progeny when females mated to control males. No effects on reproduction or pathology in low- and mid-dose groups	17.5	Not run	58.5 (FEL)	Weir and Fisher (1972) (Boron as boric acid)	
	Continuous breeding protocol: I Cohabitation and fertility 20 pairs/group (dosed), 40 pairs/group (control), CD-1 mouse, dietary, paired for 14 wk of breeding (F0)	M: 0, 26.6 111, 220 F: 0, 31.8 152, 257	At high-dose, no progeny produced (FEL). At mid-dose, progressive fertility and reproductive indices decreased with subsequent matings. At low-dose, no treatment-related effects	26.6	Not run	111	NTP (1990b); Fail et al. (1991) (Boron as boric acid) Males more sensitive species	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
	Continuous breeding protocol : II Multigeneration reproductive toxicity (F1) 20 male/20 female/group (dosed), 40 male/40 female (control), CD-1 mouse, dietary, up to 27 wk	M: 0, 26.6 111, 220 F: 0, 31.8, 152, 257	At low-dose, increased weights of uterus, kidney and adrenal glands, shortened estrus cycle in F1 females. No fertility effects. Decrease in mean F2 pup weights, Only low-dose tested; insufficient or no F1 mice from mid- and high-dose groups, respectively	None	Not run	26.6	NTP (1990b); Fail et al. (1991) (Boron as boric acid) LOAEL is lowest dose tested. Males more sensitive species	
Carcinogenic	None							
			2. Inhalation (mg/m^3)[a]					
Acute	Rats, mice guinea pigs (sex and species not reported; 10−15/group). Exposure duration either 7 hr for 1 d or 7 hr daily for 2 d; cages used either continuously for 7 hr or substituted (with clean cages) every 2 hr due to formation of irritant and corrosive oily decomposition products depositing on cage surfaces.	BCl_3 air nominal concentrations of 20, 50, and 85 or 100 ppm (4.2, 10, 18 and 20 mg/m^3).	100% (10/10) mortality at 20 and 50 ppm in rats and mice, 30% (3/10) mortality in rats and 100% (10/10) mortality in mice at 85 ppm, all guinea pigs (10/10) survived at all doses, following 7-hr continuous exposure. At 100 ppm, 14/15 mice and 10/10 guinea pigs died. Pathology showed chemical irritation to lungs and skin surfaces (paws, mouth) directly exposed to cage surfaces. No mortality at any dose in rats whose cages were cleaned every 2 hr	Not determined	Not run	4.2 (FEL)	Stokinger and Spiegl (1953)[e] Most mortality attributed to contact with deposited decomposition products. BCl_3 used as chemical intermediate in "special processes" in the production of uranium	

Table 2. Potentially Relevant Data for Boric Acid and Boron Compounds

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes
Subchronic	4−70 albino male and female rats for 10−24 wk	0, 24, 54, 146	No effects on a variety of endpoints, at 24 mg/m^3, increase in urinary creatinine	None	Not run	24	Wilding et al. (1959) (Boron as boron oxide aerosols)	
	3 dogs (sex and species not reported), 23 wk	0, 18	No effects	18	Not run	None	Wilding et al.(1959) (Boron as boron oxide aerosols)	
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure. FEL = frank effect level.
[b]NOAEL estimated by study authors.
[c]U.S. EPA (2004) used $BMDL_{05}$ calculated by Allen et al. (1996) from the combined data of Price et al. (1996a) and Heindel et al. (1992) to derive the RfD for IRIS.
[d]U.S. EPA (2004) IRIS used to derive the RfD; PS = Principal studies.
[e]Not discussed in the IRIS Toxicological Profile (U.S. EPA, 2004).

Table 3. Potentially Relevant Data for Hydrogen Chloride

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes
Human								
1. Oral (mg/kg-d)[a]								
None								
2. Inhalation (mg/m^3)[a]								
Acute	Number, gender, and duration not reported	7−150	7 mg/m^3 = no irritation, 15 mg/m^3 = irritation of mucous membrane, 75−150 mg/m^3 = intolerable irritation	7 mg/m^3	Not run	15	Stahl (1969)	
	5 male/5 female, controlled human exposure, 45 min	1.2 or 2.7	No effects on pulmonary function	2.7 mg/m^3	Not run	None	Stevens et al. (1992)	
Animal								
1. Oral[a]								
Subchronic	Wistar rats. Number and sexes varied by experiment. 7, 9, and 12 wk dietary exposure	Dietary pH 1.8−5.9	pH 2.8 = decreased plasma pH pH 2.54 = 3/8 rats died	pH = 3.09	Not run	pH = 2.8	Upton & L'Estrange (1977)	
2. Inhalation (mg/m^3)[a]								
Subchronic	31 male/31 female/group Sprague-Dawley and Fischer 344 rat, 6 hr/d, 5 d/wk, 90 d	HEC = 0, 6.1, 12.3, 30.5	Minimum to mild rhinitis, lesions in nasal cavity	None	Not run	HEC = 6.1	Toxigenics (1984)	

Table 3. Potentially Relevant Data for Hydrogen Chloride

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes
	31 male/31 female/group B6C3F$_1$ mouse, 6 hrs/d, 5 d/wk, 90 d	HEC = 0, 6.1, 12.3, 30.5	Eosinophilic globules in epithelial lining of nasal tissue	None	Not run	HEC = 6.1	Toxigenics (1984)	
Chronic	**100 male/100 female/group Sprague-Dawley rat, 6 hrs/d, 5 d/wk, lifetime**	**HEC = 0, 6.1**	**Epithelial or squamous hyperplasia in nasal mucosa**	**None**	**Not run**	**HEC = 6.1**	**Albert et al. (1982); Sellakumar et al. (1985). Only one dose tested. Used to derive U.S. EPA (1995) RfC**	**PS[c]**
Developmental	8−15 rat (strain and sex not reported), F0: 1 hr (before mating), F1: age of 2−3 mo.	450 (F0) 52 (F1)	F0: Mortality, severe dyspnea, cyanosis; F1: Abnormalities in organs	None	Not run	None	Pavlova (1976) Data poorly reported; no control group	
	Number not identified, Female rat (strain and number not identified), 1 hr (before mating)	450	Mortality in 20−30% of rats, decrease in blood oxygen saturation, kidney, liver, spleen damage	None	Not run	None	Pavlova (1976) Data poorly reported; no control group	

[a]Dosimetry, NOAELs, BMDL/BMCLs, and LOAELs are converted to human equivalent dose (HED in mg/kg-day) or human equivalent concentration (HEC in mg/m^3) units. HECs are noted for inhalation studies. Oral animal studies used feed or daily gavage as the route of administration; therefore, the HEDs are equivalent to the animal daily doses for noncancer effects.
[b]Not reported by the study author but determined from data. FEL = frank effect level.
[c]U.S. EPA (2004) IRIS used to derive the RfD; PS = Principal study.

HUMAN STUDIES

Oral Exposure

Boron Trichloride

No oral studies of boron trichloride in humans were identified. However, accidental or other exposures are discussed below.

Boric Acid and Boron Compounds

The subchronic and chronic p-RfDs for boron trichloride are based on the IRIS RfD for boron and compounds. The IRIS toxicological review (U.S. EPA, 2004) has discussed and evaluated the oral toxicity data for boron and compounds, deriving a RfD of 0.2 mg/kg-day based on decreased fetal weights in rats following maternal dietary gestational exposure to boric acid (Price et al., 1996a; Heindel et al., 1992). Tables B1–B5, in conjunction with the study descriptions in this report, present the relevant data from these developmental toxicity studies (see U.S. EPA, 2004 for a more comprehensive review of supporting and other studies). These and other data are discussed below and summarized in Table 2.

WHO (1998) and U.S. EPA (2004) summarized information concerning ingestion of boric acid and other boron compounds through accidental poisonings and other occurrences. Symptoms of boron poisoning include vomiting, abdominal pain, diarrhea, lethargy, headache, lightheadedness, and rash. The minimum lethal dose of boric acid by oral exposure was approximately 15−20 g in adults, 5−6 g in children, and 2−3 g in infants.

Baker et al. (1986) reported symptoms of boron toxicity in two infant siblings (gender not reported) who ingested formulas accidentally prepared from a boric acid eyewash solution. Ingested doses were estimated at 30.4−94.7 mg-Boron/kg-day (mg-B/kg-day). The infant whose ingestion was estimated at 30.4 mg-B/kg-day had serum concentrations of 9.79 mg-B/mL and an initial face and skin rash but later became asymptomatic. The other infant who ingested about 94.7 mg-B/kg-day had a serum boron concentration of 25.7 mg-B/mL, with symptoms of diarrhea, erythema of the diaper area, and vomiting.

O'Sullivan and Taylor (1983) reported seizures and other effects in seven infants (gender not reported) who ingested boron in a honey-borax mixture that had been applied to their pacifiers. Borax is hydrated sodium borate ($Na_2B_4O_7 \cdot 10H_2O$). However, the medical records of five of the infants suggested that they may have had familial reduced convulsive thresholds. When the honey-borax treatment ended, the seizures stopped as well. The collected data on presumptive boron ingestion and measured serum boron concentrations (details of analytic methods not provided) were not internally consistent and did not conform to what was known about boron toxicokinetics and blood concentrations.

Boron compounds have been used for a variety of medical and nonmedical purposes over the years. Culver and Hubbard (1996) reported daily doses in the range of 25−35 mg-B/kg administered to patients (number and gender not reported) undergoing boron neutron capture therapy for brain tumors (duration of exposure not reported). Nausea and vomiting occurred at 25 mg-B/kg, and additional symptoms, noted at 35 mg-B/kg, included skin flush. One patient exhibited severe dermal and gastrointestinal (GI) symptoms after subcutaneous infusion of a boric acid solution (70 mg-B/kg). After hydration and diuresis, the patient recovered.

In the 19th Century, boron was used to treat epilepsy, malaria, urinary tract infections, and exudative pleuritis. It was administered to treat epilepsy at daily doses ranging from 2.5−24.8 mg-B/kg-day (Culver and Hubbard, 1996). Clinical signs and symptoms of toxicity in patients (number and gender not reported) given ≥5 mg-B/kg-day included indigestion, dermatitis, alopecia, and anorexia. One 19th Century adult male epilepsy patient, for whom data were reported, developed indigestion, dermatitis, and anorexia when treated at a daily dose of 5.0 mg-B/kg-day for 15 days (Desage, 1923). When this dose was reduced to 2.5 mg-B/kg-day, the symptoms disappeared. In other cases, no symptoms were reported in subjects ingesting less than 3.68 mg-B/kg-day. Based on the human data summarized, Culver and Hubbard (1996) concluded the NOAEL for human exposure to boron compounds was about 2.5 mg/kg-day.

Scialli et al (2010) published an extensive review of the human data from a series of 17 peer-reviewed papers presenting an evaluation of data from Chinese boron workers with biological boron measurements higher than had been reported previously in humans. Though this evaluation included mixed inhalation and oral exposures, the data are more relevant to a RfD because the predominant route was via oral exposure. These papers, which were published subsequent to the IRIS review (U.S. EPA, 2004), were the first to include analyses of semen characteristics and, thus, provided more sensitive metrics for identifying male reproductive effects. Among the nearly 1000 male workers studied, a subset of 16 was identified as having unusually high boron exposures in drinking water, along with their occupational exposures, resulting in total mean daily exposures of 125-mg boron (1.8 mg/kg-day). The only change noted among exposed workers (75) with mean daily exposures of 31.3-mg boron (0.45 mg/kg-day) was a small but statistically significant reduction in sperm Y:X ratio, when compared to people in the two control groups with total mean daily boron exposures of 4.25 mg and 1.40 mg (0.06 and 0.02 mg-B/kg-day). However, there appeared to be no relationship between sperm Y:X ratio and biological concentrations of boron within the exposure groups, suggesting that Y:X ratio was more related to group membership than to boron exposure. In addition, the exposed workers exhibited none of the reproductive effects consistently reported among experimental mice, rats, and dogs, and none of these experimental animals exhibited dose-related changes in fetal gender ratios, or any other effect suggestive of a reduced sperm Y:X ratio. Although 0.45 mg/kg-day is identified as a LOAEL for reduced sperm Y:X ratio, Scialli et al. (2010) stated that "Y:X ratio is not known to be associated with impaired semen quality, reproductive success, or offspring health" and concluded that "there is no clear evidence of male reproductive effects attributable to boron in this study of highly exposed workers." Thus, these findings are consistent with those of earlier human studies, summarized above and used in the IRIS assessment, which used much less defined human metrics of reproductive effects among workers with smaller occupational exposures to boron compounds.

Hydrogen Chloride

In both humans and animals, the toxicity of HCl following ingestion has been due to local effects on the mucous membranes at the site of absorption (HSDB, 2011c). In case reports of patients who have swallowed HCl—either accidentally or intentionally—the primary characteristics have been massive necrosis in the esophagus, stomach, duodenum, and pancreas; in approximately half of these cases the patient died (HSDB, 2011c). WHO (1982) noted that the concentration of the HCl solution following ingestion was more important than the volume with regard to both the severity of symptoms and the outcome. Potential oral toxicity of HCl based on its pH is discussed in a subsequent section of this review.

Inhalation Exposure

Boron Trichloride

No inhalation studies of boron trichloride in humans were located in the literature. Winker et al. (2008) reported on potentially genotoxic effects among semiconductor workers, who were exposed to boron trichloride and boron trifluoride in complex mixtures of chemical waste. Frequency of micronuclei was significantly higher among exposed workers than among controls, and this frequency was reduced to control levels 12 years after exposure control measures were instituted. However, air monitoring both before and after institution of the exposure controls showed that worker exposures to boron trichloride and boron trifluoride were consistently below detection limits, providing no quantitative data that might be useful for deriving toxicity values.

Boric Acid and Boron Compounds

The IRIS toxicological review (U.S. EPA, 2004) has discussed human inhalation toxicity data for boron and compounds. Overall, well-conducted occupational epidemiology studies showed few chronic effects following inhalation exposure to boric acid and other boron compounds in work environments. Some studies found acute irritation of mucous membranes of the eyes and upper respiratory tract during workplace exposure. However, the studies were conducted in mining and manufacturing facilities with concomitant exposures to other chemical compounds, which might have confounded the association between health outcomes and exposure to boron compounds.

Birmingham and Key (1963) investigated the respiratory and irritant effects of occupational exposure to boron compounds in a borax mining and production facility. While specific quantitative data were not provided, worker complaints of dermatitis, nasal irritation, nose bleeds, cough, and shortness of breath were associated with boron dust concentrations (not measured) that were sufficiently elevated to interfere with normal visibility.

Ury (1966) used a cross-sectional study design with 629 workers to assess respiratory effects using data collected from questionnaires, spirometry, and roentgenography. The study was inconclusive, but Ury (1966) did report finding suggestive evidence for an association between respiratory effects and inhalation exposure to dehydrated sodium borate dust. Ury's analysis was based on focused expiratory volume (FEV) measures and questionnaire data on respiratory symptoms in a subgroup of 82 men working for at least 1 year in jobs with elevated boron exposure (calcining and fusing processes) as compared with 547 men in other employment categories.

Garabrant et al. (1984, 1985) studied a group of 629 workers (93% of those eligible) employed for a minimum of 5 years at the plant, who worked at jobs with borax exposures. Approximately 92% of study participants were white males, 4% were nonwhite males, and 4% were women, with a mean age of 40.2 years. Workers were assigned to one of four borax exposure categories (mean concentrations in ascending order of 1.1-, 4.0-, 8.4-, or 14.6-mg/m^3 borax, respectively) and assessed for frequency of reported acute and chronic respiratory symptoms, using questionnaire response data. Statistically significant, positive dose-related trends were reported for the following (in order of decreasing frequency): dryness of mouth, nose, or throat; eye irritation; dry cough; nose bleeds; sore throat; productive cough; shortness of breath; and chest tightness. There was a wide range of variability in the frequency of symptoms within exposure groups; in the highest exposure group, symptoms frequency ranged from 5% to

33%. Pulmonary function was unaffected by borax exposure, and no differences in the results of chest X-rays were noted between groups. The study authors concluded that exposure to borax at the concentrations reported in this study may cause respiratory irritation, which could lead to chronic bronchitis without impairment of pulmonary function.

In a subanalysis, Garabrant et al. (1984) reported that 113 workers (91% white males, 5 nonwhite males, 4% women) in job categories with boric acid or boron oxide exposures had statistically significantly higher rates of eye irritation; dryness of mouth, nose, or throat; sore throat; and productive cough, as compared with 214 workers who had not been occupationally exposed to either boric acid or boron oxide but had held at least one job that involved low exposure to borax. Mean combined exposure to boron oxide and boric acid was 4.1 mg/m^3 (range = 1.2 to 8.5 mg/m^3). Garabrant et al. (1984) concluded that the inhalation of boron oxide and boric acid produced upper respiratory and eye irritation at airborne concentrations less than 10 mg/m^3.

Wegman et al. (1994) conducted pulmonary function retesting of 336 participants in the Garabrant et al. (1985) study, 7 years following the original study. Of these, 306 had "acceptable" pulmonary function test results in both studies. No information on the genders or ethnicities of the subjects was given. Mean age was 44 years. The rates of decline in FEV_1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) were very similar to those expected because of aging, based on national population data. Thus, Wegman et al (1994) concluded that cumulative chronic borate exposure over the years 1981−1988 was not related to the change in pulmonary function. Wegman et al. (1994) further examined the association between the occurrence of episodes of acute respiratory symptoms, exposure concentrations, and the approximate time between symptoms onset and the beginning of exposure during the work shift in a subgroup of 106 subjects. Exposure was assessed by personal aerosol monitors. Incident rate for each symptom was expressed as the ratio of the number of symptomatic episodes to the number of person-hours for which the individual was exposed. Risk ratios—defined as the ratio of the probability of symptoms in the exposed to the probability in the comparison group—were estimated for each symptom. Categories of increasing exposure concentrations then were defined, and the incidence was estimated within each category. To adjust for confounding due to smoking, age, and recent colds, the associations then were estimated in a series of logistic regression models. A separate model was fitted to the data for each of the five most common symptom outcomes. Symptoms rate ratios were then compared between exposed and comparison populations, and a one-tailed binomial distribution test for significance was performed. Statistically significant ($p < 0.001$) exposure-related increases in eye, nasal, and throat irritation; cough; and breathlessness were associated with elevated borate exposure, assessed using either a 6-hour or 15-minute time-weighted average. Nasal irritation appeared to increase most rapidly with increasing exposure, with notable increases starting at about 5 mg/m^3 for either exposure duration. The follow-up findings were consistent with those from the earlier study showing irritation and upper respiratory tract symptoms in the absence of exposure-related decreases in pulmonary function, suggesting that the symptoms resulted from acute exposures and resolved when exposures were terminated.

Tarasenko et al. (1972) reported low sperm count, reduced sperm motility, and elevated fructose content of seminal fluid in semen analysis of 6 workers who were part of a group of 28 male Russian workers exposed for 10 or more years to high levels of vapors and aerosols of boron salts (22−80 mg/m^3) during the production of boric acid. The results indicated that the

exposed workers had decreased sexual function compared with 10 workers who had no contact with boric acid. However, Tarasenko et al. (1972) reported no differences in data from wives of the men in the exposed and control groups. The precise nature of the data for wives is not known. This study was published in the Russian literature, and cited by Whorton et al. (1992, 1994a,b). This study was judged to be of limited value for toxicity determinations due to the small sample size; sparse details on subjects regarding smoking habits, diet, other chemical exposures; and lack of methodology information on semen analysis (U.S. EPA, 2004). However, the results suggested that airborne occupational exposure to boron salts in the range 22−80 mg/m^3 might cause decreased sexual function in male workers.

In response to the Tarasenko et al. (1972) report and the reports of reproductive effects in animal studies, Whorton et al. (1992, 1994a,b) initiated a controlled epidemiology study of reproductive effects in U.S. workers exposed to sodium borates. The site of the study was a borax mining and production facility in the United States with 542 men participating (72% of the 753 eligible male employees) by answering a questionnaire Whorton et al. (1994a,b). The median exposure of the men in the study was approximately 2.23 mg/m^3 sodium borate (roughly 0.31 mg-B/m^3), with an average length of employment of 15.8 years. Reproductive function was assessed by (1) comparing the number of live births by workers' wives during the workers' employment period (+9 months following commencement of work through +9 months following termination of work) to standardized birth ratios (SBRs) in national fertility tables for U.S. women, matched on maternal age, race, parity, and calendar year; and (2) comparing the gender ratio in the workers' offspring with national gender ratios compiled for the United States.

Overall, the study participants were more fertile than the national sample, with 529 observed births vs. 466.6 expected births, SBR = 113, $p < 0.01$ (Whorton et al., 1994a,b). An excess of births in the study population occurred even though study males had a 5-fold higher rate of vasectomies (36% vs. 7% national average). No exposure-response relationship in SBR was noted when mean exposure concentrations were divided into five equal-size categories ranging from <0.82 mg/m^3 to 5.05 mg/m^3. The SBR was statistically significantly elevated for both the low- and high-dose groups and was close to expected for the three mid-dose groups. An examination of SBR for all participants by 5-year increments from 1950 to 1990 showed no statistically significant trend in either direction over time. Although there was an increase in percent female offspring in the worker cohort (52.7% vs. 48.8% in controls), this finding was not statistically significant and appeared to be unrelated to paternal airborne exposure to sodium borate. Interpretation of study results is made difficult by the lack of a local or matched control group and the use of an insensitive measure of sexual function.

In another study, Whorton et al. (1992) assessed 68 female workers for reproductive function. Although the SBR for live births was <100, the reduction in birth rate was not statistically significant. No statistically significant differences in birth rates or offspring gender ratios were observed between exposed and control groups when the results were analyzed by exposure categories. Whorton et al. (1992) concluded that exposure to inorganic borates did not appear to adversely affect fertility in the population studied. However, the small sample size of exposed women limited the sensitivity of the study.

Swan et al. (1995) investigated the relationship between exposure to chemical and physical agents used in the semiconductor manufacturing industry and incidence of spontaneous abortion in female employees at 14 industry plants between 1986 and 1989. The study

population consisted of 904 current and former female employees who became pregnant while working at one of these facilities. Exposure classifications were based on jobs held at conception and exposures to specific agents during the first trimester. No statistically significant association was found between exposure to boron and spontaneous abortion risk ($p > 0.05$). This study was limited by a number of factors—including co-occurring exposures to numerous chemicals and lack of dose-response information.

Hydrogen Chloride

IRIS (U.S. EPA, 1995) has evaluated the inhalation toxicity data for HCl, deriving a RfC of 0.02 mg/m^3, based on hyperplasia of the nasal mucosa, larynx and trachea in rats (Sellakumar et al., 1985;[2] Albert et al., 1982). Relevant data are summarized below.

HCl is intensely irritating to the mucous membranes of the eyes, nose, throat, and respiratory tract (HSDB, 2011c). Brief exposure to 35 ppm (52 mg/m^3) caused throat irritation as well as sneezing, laryngitis, chest pain, hoarseness, and a feeling of suffocation (WHO, 1982). The greatest impact was on the upper respiratory tract; exposure to high concentrations have led to rapid swelling and spasm of the throat, and suffocation. Symptoms of high-exposure concentrations include immediate onset of rapid breathing, blue coloring of the skin, and narrowing of the bronchioles. In both humans and animals, the toxicity of HCl after inhalation is due to the local effect on the mucous membranes at the site of absorption.

Epidemiologic studies examining the relationship between HCl vapor exposure among workers and risk of lung or brain cancer showed no association, using a variety of exposure metrics (IARC, 1992).

According to Stahl (1969), there were no known systemic effects of HCl inhalation in humans (number, gender, and duration not reported), and only local effects on membranes of the eyes and upper respiratory tract have been observed. Irritation was not reported at airborne concentrations of approximately 7 mg/m^3 (4.7 ppm). An airborne concentration of 15 mg/m^3 (10 ppm) caused irritation of the mucous membranes following initial exposure; however, tolerance or acclimation occurred with increasing exposure duration. At exposure concentrations ranging from 75−150 mg/m^3 (50.3−100.5 ppm), irritation was reported as "intolerable," and no adaptation occurred. These data suggest a short-term LOAEL of 15 mg/m^3 for transient irritation of the mucous membranes of the eyes and upper respiratory tract among humans, with a NOAEL of 7 mg/m^3.

In a controlled human exposure study, Stevens et al. (1992) exposed five asthmatic volunteers per gender to 0.8- (1.2 mg/m^3) or 1.8-ppm (2.7 mg/m^3) HCl for 45 minutes. Pulmonary function tests were performed immediately after exposure, and results were compared to baseline levels. No exposure-related effects were reported in pulmonary function tests or in symptoms, including forced expiratory volume in 1 second, forced vital capacity, maximal flow at 50 and 75% of vital capacity, respiratory resistance, and peak flow. These data suggest a 45-minute NOAEL of 2.7 mg/m^3 among asthmatic humans, with no LOAEL.

[2]U.S. EPA (1995) Summary text for HCl on IRIS incorrectly cites this as Sellakumar et al., 1994.

ANIMAL STUDIES

Oral Exposure

Boron Trichloride

No studies were identified.

Boric Acid and Boron Compounds

The IRIS toxicological review (U.S. EPA, 2004) has discussed and evaluated oral toxicity data for boron and compounds, deriving a RfD of 0.2 mg/kg-day based on decreased fetal weights in rats following maternal dietary gestational exposure to boric acid (Price et al., 1996a; Heindel et al., 1992). Appendix B presents the relevant data from these developmental toxicity studies (see Tables B.1−B.5). These data provide the basis for the p-RfDs for boron trichloride. Other data are described below.

Weir and Fisher (1972) conducted subchronic and chronic duration studies with Sprague-Dawley rats and dogs, as well as a follow-up subchronic study in dogs. In the subchronic rat study, Weir and Fisher (1972) administered boric acid (purity not reported) in the diet to 10 rats/sex/group for 90 days at concentrations of 0-, 52.5-, 175-, 525-, 1750-, or 5250-ppm boron. These dietary concentrations are approximately equivalent to 0, 2.6, 8.8, 26.3, 87.5, and 262.5 mg-B/kg-day, respectively, estimated using an EPA (1988) standard adjustment factor of 0.35 kg for body weight and 0.05 for the food factors. At the highest dose tested, mortality was observed in all rats of both sexes, and complete testicular atrophy was observed in all males at the second highest dose. Other signs of toxicity in the two highest-dose groups included rapid respiration, eye inflammation, swelling of the paws, and desquamation of the skin on paws and tails.

Weir and Fisher (1972) evaluated statistical significance for body- and organ-weight changes using conventional statistical tests comparing treated and control rats and using $p < 0.05$ as the level of significance. No further description of statistics was reported. At the second highest dose of boric acid (87.5 mg/kg-day), body weights were statistically significantly reduced (44% decrease in males and 13% decrease in females as compared with respective controls). In this dose group, the following significant organ-weight changes relative to controls were also observed: (1) decreased absolute kidney, spleen, liver, adrenal, and testis weights in males; (2) decreased absolute spleen, liver, and ovary weights in females; (3) decreased relative liver and testis weights in males and decreased relative liver weights in females; (4) increased relative brain and thyroid weights in males and females and increased adrenal weight in males. At lower doses, no consistent treatment-related organ-weight effects were observed. Microscopic examination showed complete testicular atrophy at 87.5 mg-B/kg-day in all males and partial testicular atrophy at 26.3 mg-B/kg-day in one male. No treatment-related effects were observed at the lowest dose tested. Weir and Fisher (1972) did not identify a LOAEL or a NOAEL. However, a 90-day LOAEL and NOAEL of 26.3 and 8.8 mg-B/kg-day, respectively, are considered for testicular atrophy in male rats.

In the subchronic dog study, Weir and Fisher (1972) fed groups of beagles (5/sex/group) boric acid (purity not reported) for 90 days at dietary concentrations, of 0-, 17.5-, 175-, or 1750-ppm boron. These dietary concentrations are equivalent to 0, 0.33, 3.9, and 30.4 mg-B/kg-day in male beagles, and 0, 0.24, 2.5, and 21.8 mg-B/kg-day in females, based on measured body weight and food consumption. With the exception of one high-dose male who died during the study, no mortality or clinical signs of toxicity were observed. As in rats (i.e.,

Weir and Fisher, 1972) and mice (i.e., NTP, 1987; Dieter, 1994), the testes were the primary target of boron toxicity. Decreases in both absolute and relative testes weights were observed in the high-dose group. Microscopic pathology revealed severe testicular atrophy in all high-dose male dogs, with complete degeneration of the spermatogenic epithelium in four dogs. No testicular lesions were found in the lower-dose groups. Accumulation of hemosiderin pigment in the liver, spleen, and kidney—indicating breakdown of red blood cells—was observed in high-dose male and female beagles treated with boric acid. Relative thyroid weights in males were decreased, and liver weights in females were increased at the high dose. Some pathology in the thyroid and adrenal glands of high-dose females also was observed. Weir and Fisher (1972) did not identify a NOAEL. However, based on testicular effects, breakdown of red blood cells, and thyroid and adrenal gland pathology, 90-day LOAELs of 30.4 and 21.8 mg-B/kg-day and NOAELs of 3.9 and 2.5 mg-B/kg-day in male and female beagles, respectively, are considered for this study.

In a 13-week study, NTP (1987; Dieter, 1994) fed groups of 10 male and 10 female B6C3F_1 mice diets containing 0-, 1200-, 2500-, 5000-, 10,000-, or 20,000-ppm boric acid (>99.7% purity), calculated by the study authors to correspond to 0, 34, 70, 141, 281, and 563 mg-B/kg-day for males and 0, 47, 97, 194, 388, and 776 mg-B/kg-day for females, respectively. At the highest doses, greater than 60% mortality was observed, and clinical signs of toxicity included hyperkeratosis and acanthosis of the stomach. At dietary concentrations 5000 ppm and greater, degeneration or atrophy of the seminiferous tubules was observed in males, and weight gain was decreased in animals of both sexes. NTP (1987; Dieter, 1994) did not identify a NOAEL or LOAEL. Based on histopathology in the seminiferous tubules, the 13-week NOAEL and LOAEL are 70 and 141 mg-B/kg-day, respectively, in male mice.

NTP (1987; Dieter, 1994) also fed male and female B6C3F_1 mice (50/sex/group) a diet containing 0-, 2500-, or 5000-ppm boric acid (>99.7% purity) for 103 weeks. These concentrations were equivalent to boric acid doses of approximately 0, 275, and 550 mg/kg-day (0, 48, and 96 mg-B/kg-day), respectively, calculated based on food consumption values obtained during Week 4. These doses for the chronic bioassay were selected from the subchronic study. Tests of significance included the product-limit procedure by Kaplan and Meier for probability of survival, Cox's test for equality, and Tarone's life-table test for possible dose-related trends in survival. For other adverse effects, Fisher's Exact test for pair-wise comparisons, Cochran-Armitage test for dose-related trends, life-table analysis adjusting for intercurrent mortality, and incidental tumor analysis were conducted. Level of significance was $p < 0.05$.

Survival of the treated male mice was statistically significantly lower than that of controls after Week 63 in the low-dose group and after Week 84 in the high-dose group, but female mortality was unaffected by treatment (NTP, 1987; Dieter, 1994). The sensitivity of the carcinogenicity evaluation in males may have been compromised by the high mortality rates in all groups including controls. Mean body weights of high-dose mice were 10−17% lower than those of controls. Pathological findings were limited to testicular atrophy and interstitial cell hyperplasia in high-dose males and a dose-related increase in the incidences of splenic lymphoid depletion, also in males. No other treatment-related, nonneoplastic lesions were observed. The study authors did not identify a NOAEL. However, based on increased mortality in male mice, 48 mg-B/kg-day is identified as a FEL, with no associated NOAEL.

An increased incidence in hepatocellular carcinoma was noted in low-dose males relative to controls (5/50, 12/50, 8/49 for control, low-, and high-dose groups, respectively) as was the combined incidence of adenoma or carcinoma (14/50, 19/50, 15/49 for control, low-, and high-dose groups, respectively). The increases were statistically significant by life-table tests but not by incidental tumor tests. NTP (1987) considered the incidental tumor test to be more suitable for statistical analysis because liver tumors were not associated with mortality and their incidences were lower than, or within the range of, historical control tumor rates for male mice in the laboratory. Other tumors were not considered to be test compound related. No tumors were observed in female mice. NTP (1987) concluded that boric acid was not carcinogenic in mice under the conditions of the study.

In a chronic rat study, Weir and Fisher (1972) fed Sprague-Dawley rats (35/sex/group and 70/sex/control group) a diet containing 0-, 117-, 350-, or 1170-ppm boron as boric acid (purity not reported) for 104 weeks. These dietary concentrations correspond approximately to 0, 5.9, 17.5, and 58.5 mg-B/kg-day, estimated by using an EPA (1988) standard adjustment factor of 0.35 kg for body weight and 0.05 for the food factors. In the 58.5-mg/kg-day group, signs of clinical toxicity were observed, and decreased body-weight gain was accompanied by reduced food consumption. Testicular atrophy was observed in all high-dose (58.5-mg/kg-day) males at 6, 12, and 24 months. The seminiferous epithelium was atrophied, and the tubular size in the testes was decreased. Absolute and relative testes weights were reduced, and relative brain and thyroid weights were increased in this dose group. Weir and Fisher (1972) reported that no other effects were observed in the highest-dose groups, and no adverse findings of any sort were observed at the two lowest doses. Weir and Fisher (1972) identified a chronic NOAEL of 17.5 mg-B/kg-day for testicular effects, decreased body-weight gain, and signs of clinical toxicity. A LOAEL of 58.5 mg/kg-day is identified for this study, based on the same adverse effects. The lack of carcinogenic findings in this study led NTP (1987) to conclude that there were no carcinogenic effects of boric acid in rats.

In the chronic dog study, Weir and Fisher (1972) administered boric acid (purity not reported) by dietary admix to groups of beagles (4/sex/group) at concentrations of 0-, 58-, 117-, or 350-ppm boron (0, 1.4, 2.9, and 8.8 mg-B/kg-day, respectively) for 2 years (Weir and Fisher, 1972). Interim sacrifice was at 52 weeks. Following 104 weeks of exposure, a subgroup of beagles was given a 13-week "recovery" period prior to terminal sacrifice. Sperm samples used for counts and motility testing were taken only from the control and high-dose male dogs immediately prior to the 2-year sacrifice. Statistical tests were not conducted. Mortality over the course of the study did not appear to be treatment related. Weir and Fisher (1972) considered neither semen characteristics nor histopathology of any target organ, including tumors, to be associated with boric acid administration. The study authors identified a 2-year NOAEL of 8.8 mg/kg-day, the highest dose tested, based on no "apparent" effects on body weight, organ weights, and necropsy findings as compared with controls in male or female beagles. A LOAEL is not identified in this study.

In a follow-up dog study, Weir and Fisher (1972) administered boric acid (purity not reported) in the diet to groups of 4 beagles (4/sex/group) at concentrations of 0- and 1170-ppm boron (29.2 mg-B/kg-day) for up to 38 weeks. Interim sacrifice for two beagles in each group was at 26 weeks; terminal sacrifice was at 38 weeks. One of the two beagles in each 38-week subgroup was sacrificed after a 25-day "recovery" period. In controls, one of the two males sacrificed at 26 weeks had decreased spermatogenesis, and no effects were reported in the other

male. One control male sacrificed at 38 weeks had decreased spermatogenesis, and the other had testicular atrophy. In the treated beagles, both males sacrificed at 26 weeks showed evidence of severe testicular atrophy and spermatogenic arrest. The male sacrificed at 38 weeks showed similar testicular effects. Absolute and relative testes weights also were decreased in these beagles. Following the "recovery" period, absolute and relative testes weights were similar between control and treated dogs, and microscopic examination revealed the presence of moderately active spermatogenic epithelium in the single treated dog sacrificed at this time. The study authors suggested that boron-induced testicular degeneration in dogs may be reversible upon cessation of exposure, although this statement was based on findings in only one beagle. It is difficult to interpret the findings of this follow-up study due to the small number of animals examined and the relatively short time duration of exposure as compared to the 2-year study. Statistical tests were not conducted because of the low number of animals. Nonetheless, based on testicular effects, the study authors identified a 26-week and 38-week LOAEL of 29.2 mg-B/kg-day for beagle dogs.

Numerous studies have been conducted investigating the developmental and reproductive toxicity of oral boric acid and other boron compounds. Heindel et al. (1992, 1994) and NTP (1990a) administered boric acid (98−99% purity) in the diets to timed-mated female Sprague-Dawley rats (29/group) at concentrations of 0, 0.1, 0.2, or 0.4% from Gestation Days (GDs) 0−20 (see Tables B.1 and B.2). Based on measured food consumption, the diet provided about 0-, 78-, 163-, or 330 mg-Boric acid/kg-day (equivalent to 0, 13.6, 28.5, and 57.7 mg-B/kg-day). Additional groups of 14 female rats each received boric acid at 0 or 0.8% in the diet (0 or 94.2 mg-B/kg-day) only on GDs 6−15. Food and water intake and body weights—as well as clinical signs of toxicity—were monitored throughout pregnancy. On GD 20, the rats were sacrificed; the livers, kidneys, and intact uteri were weighed; corpora lutea were counted; and maternal kidneys were assessed histopathologically. Live fetuses were removed, weighed, and subsequently examined for external, visceral, and skeletal malformations. The study followed GLP standards.

Bartlett's test was used to examine homogeneity of variance, and General Linear Models (GLM) test for linear trend was used to determine the significance of dose-response relationships (Heindel et al., 1992, 1994). The significance of dose effects, replicate effects, and (dose × replicate) interactions was determined by analysis of variance (ANOVA). When ANOVA revealed a statistically significant ($p < 0.05$) dose-response effect, Williams or Dunnett's multiple comparison tests were used to compare each exposed group to the concurrent control group. One-tailed tests were used for all pair-wise comparisons except maternal body and organ weights, water and feed consumption, and fetal body weight.

Heindel et al. (1992, 1994) and NTP (1990a) reported that no maternal mortality was observed, and neither maternal food nor water intake differed statistically significantly ($p < 0.05$) from controls—except in the 0.8% (94.2 mg-B/kg-day) group, where both intakes decreased on GDs 6−9 and increased on GDs 15−18. Statistically significant maternal effects attributed to treatment in rats were (1) a decrease in body-weight gain during treatment at feed concentrations of 0.4% (57.7 mg-B/kg-day) and greater; (2) an increase in relative liver and kidney weights at 0.2% (28.5 mg-B/kg-day) and greater boric acid in feed; and (3) an increase in absolute kidney weight at 0.8% (94.2 mg-B/kg-day). Minimal nephropathy was observed in maternal kidneys, but the incidence and severity were not dose related. Pregnancy rates ranged between 90 and 100% for all groups. At the 0.8% (94.2 mg-B/kg-day) dose, prenatal mortality was increased, as

evidenced by increased fetal resorptions, increased late fetal deaths, and decreased number of live fetuses per litter. Mean fetal body weight per litter was statistically significantly reduced ($p < 0.05$) in a dose-dependent manner in all treated groups relative to controls: 94, 87, 63, and 46% of the corresponding control body-weight means for the 13.6, 28.5, and 57.7 mg-B/kg-day groups, respectively.

At dietary concentrations of 0.2% (28.5 mg-B/kg-day) and greater, Heindel et al. (1992, 1994) and NTP (1990a) reported the following statistically significant ($p < 0.05$) effects: (1) an increase in the percentage of litters with malformed fetuses; (2) an increase in the percentage of litters with at least one malformed fetus; and (3) an increase in the incidence of litters with one or more fetuses with a skeletal malformation. At 0.2% in diet (28.5 mg-B/kg-day), malformations consisted primarily of the axial skeleton and anomalies of the eyes, the central nervous system (CNS), and the cardiovascular system. At both 0.4% (57.7 mg-B/kg-day) and 0.8% (94.2 mg-B/kg-day) dietary concentrations, the incidences of litters with one or more pups with visceral and gross malformations were statistically significantly increased ($p < 0.05$), with the most commonly-occurring malformations being enlarged lateral ventricles of the brain and agenesis or shortening of rib XIII. Based on the changes in organ weights, the study authors identified a 21-day maternal LOAEL of 28.5 mg-B/kg-day and a maternal NOAEL of 13.6 mg-B/kg-day in rats. Based on the decrease in fetal body weight on a per-litter basis in rats, the study authors identified a developmental LOAEL of 13.6 mg-B/kg-day, the lowest dose tested; a developmental NOAEL could not be determined.

In a follow-up two-phase study, NTP (1994) and Price et al. (1996a) dosed timed-mated female CD rats (60/group) from either GDs 0−20 (Phase I) or Postnatal Days (PND) 0−21 (Phase II) with dietary boric acid (99% purity) at feed concentrations of 0, 0.025, 0.05, 0.075, 0.1, or 0.2% (see Tables B.3−B.5). Equivalent daily doses were 0, 3.3, 6.3, 9.3, 13.3, and 25.0 mg-B/kg-day for dams dosed from GDs 0−20 (Phase I) and 0, 3.2, 6.5, 9.7, 12.9, and 25.3 mg-B/kg-day for dams dosed from GD 0−PND 21 (Phase II). The study was GLP-compliant. Throughout gestation, rats were monitored for body weight, clinical condition, and food and water intake. In Phase I, reproductive and teratology evaluations were conducted. In Phase II, pups were evaluated for mortality, body weight, and morphology (external, visceral, and skeletal).

In Phase I, neither maternal mortality nor clinical signs of maternal preimplantation loss were affected by treatment (NTP, 1994; Price et al., 1996a). Fetal body weights were statistically significantly decreased in the two highest-dose groups on GD 20. The incidence of external or visceral malformations and variations did not differ, either on a per-litter or per-fetus basis, between treated and control rats. However, a statistically significant increase in the incidence of fetuses with skeletal malformations or variations on a per-litter basis was observed in the two highest-dose groups. The study authors considered the increased incidence in short rib XIII to be a skeletal malformation, although they noted that others consider it a skeletal variation (Price et al., 1996a). The study authors considered a statistically significant increase in the incident of wavy ribs to be a skeletal variation. The number of rudimentary extra ribs on lumbar I decreased with increasing dose, both in terms of number of litters in which it was observed and of number of offspring per litter. These findings were not statistically significant, although there was a statistically significant trend. The biological significance of this result is not clear. Based on decreased fetal body weights, NTP (1994) and Price et al. (1996a) identified

a developmental LOAEL of 13.3 mg-B/kg-day and NOAEL of 9.6 mg-B/kg-day in rats for Phase I of this study.

In the Phase II study, neither maternal mortality nor clinical signs of maternal preimplantation loss were affected by treatment (NTP, 1994; Price et al., 1996a). In the pups, a trend test (Cochrane-Armitage) suggested a dose-related statistically significant increase in postnatal mortality during PNDs 0−4 and PNDs 0−21 but not between PNDs 4−21 (NTP, 1994; Price et al., 1996a, see Table B.4). However, the observed mortality rate in the high-dose group was within the range of historical controls for this species and strain (Charles River, 1993). According to Price et al. (1996a): "During lactation, the number and percentage of pup deaths/litter exhibited increasing trends, but the number of implantation sites/litter, cumulative offspring mortality (i.e., percentage of implantation sites) and number of live pups/litter did not differ among groups. Thus, there was no definitive evidence for an adverse effect on offspring viability from conception through weaning" (p. 181).

Pup body weights did not differ among groups during PNDs 0−21, demonstrating that the decrease in fetal body weights observed in Phase I on GD 20 did not persist during the postnatal period. The incidence of external or visceral malformations and variations did not differ, either on a per-litter or per-fetus basis, between treated and control rats. However, the percentage of pups per litter with short rib XIII (a skeletal malformation) was still elevated on PND 21 in the high-dose group. The incidence of wavy rib (a skeletal variant), observed to be statistically significantly increased in the two highest-dose groups on GD 20, did not differ from controls by the end of the lactation period. The statistically significant trend in decreased incidences of rudimentary extra rib on Lumbar I, observed on GD 20, did not occur on PND 21. Based on skeletal malformations (short rib XIII), NTP (1994; Price et al., 1996a) identified the developmental NOAEL and LOAEL for the postgestational phase (II) of this study as 12.9 and 25.3 mg-B/kg-day, respectively.

Heindel (1992, 1994) and NTP (1989) studied the developmental effects of boric acid in mice and rabbits. Groups of 28−29 CD-1 mice were exposed to boric acid (98−99% purity) in the diet on GDs 0−17 using the same experimental design as in the first Price et al. (1996a) rat study. The feed concentrations of boric acid were 0, 0.1, 0.2, or 0.4% (approximately equivalent to 0, 43.4, 79.0, or 175.3 mg-B/kg-day). Studies were GLP compliant. Tables B.6 and B.7 summarize these findings. Survival rates, pregnancy rates, and maternal weight gains corrected for gravid uterine weight were not affected by treatment. However, maternal body weights at GD 17 were statistically significantly reduced (10−15% relative to concurrent controls) in the high-dose group. The following effects were also observed in the dams: (1) statistically significant increases in relative kidney and absolute liver weights at the high-dose relative to controls; and (2) a dose-related increase in maternal renal tubular dilation and/or regeneration (0, 2, 8, and 10 animals in the 0-, 43.4-, 79.0-, and 175.3-mg-B/kg-day dose groups, respectively). The only developmental effects were statistically significant increases in the percentage of litters with one or more resorptions and in the percentage of resorptions per litter at 175.3 mg-B/kg-day. Mean fetal body weights were statistically significantly decreased in the two highest-dose groups on GD 17 relative to concurrent controls. The percentage of malformed fetuses per litter increased statistically significantly in the high-dose group, and the most frequent malformation was short rib XIII. Based on kidney effects in the dam, the study authors identified the maternal mouse 18-day NOAEL and LOAEL as 0.1% (43.4 mg-B/kg-day) and 0.2% (79.0 mg-B/kg-day), respectively. Based on a decrease in mean fetal body weights at

maternally toxic doses, the study authors identified the developmental NOAEL and LOAEL as also 43.4 mg-B/kg-day and 79.0 mg/kg-day, respectively, in mice.

Price et al. (1996b) and Heindel et al. (1994) gavaged artificially inseminated New Zealand White rabbits (30/group) with boric acid (99% purity) in an aqueous vehicle at doses of 0, 62.5, 125, or 250 mg/kg/day (0, 10.9, 21.9, and 43.7 mg-B/kg-day) on GDs 6−19 and sacrificed them on GD 30. The study followed GLP standards. Treatment-related mortality was not observed. The only clinical sign of toxicity was vaginal bleeding, noted in 2 to 11 rabbits per day in the high-dose group during the postexposure (GDs 19−30) interval. None of these rabbits carried live fetuses when sacrificed on GD 30. Decreased food intake was observed in the high-dose group on GDs 6−15, followed by a rebound in food intake in mid- and high-dose females on GDs 25−30, which was after treatment termination. Body weight on GDs 9−30 and the number of corpora lutea per dam were decreased in the high-dose group. Relative kidney weights increased in high-dose dams, but there was no change in either absolute kidney weights or in absolute and relative liver weights. At the high-dose, the following frank effects were observed: (1) a 90% resorption rate per litter compared to 6% in concurrent controls; (2) a statistically significant increase in the percentage of pregnant females with no live fetuses (73% compared with 0% in controls); and (3) a statistically significant decrease in the number of live fetuses per litter on GD 30 (2.3 fetuses/litter compared with 8.8 fetuses/litter in controls). Fetal body weights per litter at the high-dose were depressed relative to control, but, due to the small number of live fetuses in the high-dose group, this finding was not statistically significant. The incidence of malformations in live fetuses per litter was statistically significantly elevated at the high dose, primarily associated with cardiovascular defects that were predominantly located in the interventricular septum. In contrast, the incidence of skeletal malformations was comparable among groups. No reproductive or developmental effects were found in the low- and mid-dose groups. Based on clinical signs and reproductive effects in the dams and visceral malformations in the fetus, the study authors identified 14-day maternal and developmental LOAEL and NOAEL of 250 mg-Boric acid/kg-day (43.7 mg-B/kg-day) and 125 mg-Boric acid/kg-day (21.9 mg-B/kg-day), respectively, in rabbits.

In a subchronic reproductive toxicity study, Dixon et al. (1976) gave male Sprague-Dawley rats (10/group) 0, 0.3, 1.0, or 6.0 mg-B/L, as borax (11% boron, purity not given) in drinking water for 30, 60, and 90 days. Equivalent daily doses were 0, 0.042, 0.14, and 0.84 mg-B/kg-day, respectively. No changes in male fertility were observed, as assessed by breeding studies. Similarly, no effects of treatment were noted for body weight; testis, prostate, and seminal-vesicle weights; serum chemistry parameters; plasma concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH); and fructose, zinc, and acid phosphatase concentrations in the prostate. The study did not report whether GLP standards were followed. The majority of data was presented in graphical form, and statistical tests used for analysis were not given. The study authors did not identify a NOAEL. As no treatment-related effects were reported, the 30−90-day male rat NOAEL is identified as 0.84 mg-B/kg-day, the highest dose tested in this study.

In a follow-up dietary study at much higher doses, Lee et al. (1978) and Dixon et al. (1979) administered diets containing 0-, 500-, 1000-, or 2000-ppm boron (as borax; purity not reported), approximately equivalent to 0, 25, 50, and 100 mg-B/kg-day, respectively, to male Sprague-Dawley rats (18/group) for 30 or 60 days. Statistical differences between control and experimental groups were calculated using the Student's *t*-test. Level of significance was

$p < 0.05$. Although the study appears to have been well conducted, it did not report whether GLP standards were followed. In the two highest-dose groups, liver, testis, and epididymis weights were statistically significantly decreased. Although seminiferous tubule diameters showed a statistically significant dose-dependent decrease in all treatment groups, this decrease was associated only with a statistically significant loss of germinal cell elements at the two highest doses. Other effects included complete seminiferous tubule aplasia at the highest dose and statistically significant dose- and duration-dependent elevation of plasma FSH—but not of plasma LH or testosterone. Serial mating studies, analyzed using the Fisher nonparametric test with $p < 0.05$ as the level of significance, showed that fertility was reduced at the two highest doses without any concomitant changes in copulatory behavior. The study authors did not identify a NOAEL. Based on findings of tubular germinal aplasia, a NOAEL and LOAEL of 25 and 50 mg-B/kg-day, respectively, are identified for this study.

Linder et al. (1990) evaluated the time response and dose response of male rat reproductive end points after single- and repeated-dosing (14 days) via gavage administration of boric acid. Although the study did not report whether GLP standards had been followed, the experiments were conducted in EPA laboratories. In the time-response experiment, Sprague-Dawley rats (6/group) were given single doses of 0- or 2000 mg-Boric acid/kg (0 or 350 mg-B/kg, respectively) by gavage and were sacrificed at 2, 14, 28, and 57 days after dosing. In the dose-response experiment, groups of eight male rats were administered single doses of 0-, 250-, 500-, 1000-, or 2000-mg-Boric acid/kg (0, 44, 87, 175, or 350 mg-B/kg) by gavage and were sacrificed 14 days later. In both the time-response and the dose-response studies, the above doses were the total of two doses administered at 9:00 a.m. and 4:00 p.m. on the same day. The following statistical tests were performed: (1) ANOVA and Duncan's multiple range test for sperm counts; and (2) Wilcoxon scores and the Kurskal-Wallis tests for evaluation of sperm motility and morphology. The level of statistical significance was set at $p < 0.05$. No statistically significant clinical signs of toxicity were observed during the study. In the time-response study, statistically significant effects on Day 28 included an increase in abnormal caput and cauda epididymal sperm morphology, and a decreased percentage of motile cauda spermatozoa with reduced straight-line swimming velocities. The sperm parameters in all animals had returned to control values by Day 57 postdosing. In the dose-response study, adverse effects on spermiation (discharge of spermatozoa from the testis), epididymal sperm morphology, and caput sperm reserves appeared in the two highest-dose groups (175 and 350 mg-B/kg). The study authors identified a 14-day NOAEL of 87 mg/kg in male rats. Based on spermatogenic effects, a 14-day LOAEL of 175 mg/kg is identified for this study.

In a reproductive toxicity study, Weir and Fisher (1972) gave male and female Sprague-Dawley rats (8 males/group and 16 females/group) dietary boric acid (purity not given) at feed concentrations approximately equivalent to 0, 5.9, 17.5, or 58.5 mg-B/kg-day for three generations. Weir and Fisher (1972) reported no adverse effects on reproduction or gross pathology in rats in the low- and mid-dose groups. In the high-dose group, no progeny were produced, no spermatozoa were found in the atrophied testes, and females showed statistically significantly decreased ovulation. Mating high-dose females with control males resulted in no litters. Based on frank effects on fertility and accompanying changes in germinal tissues, 58.5 mg-B/kg-day is identified as a three-generation frank effect level (FEL) in rats. A three-generation NOAEL of 17.5 mg-B/kg-day is identified in rats for this study. No LOAEL is determined because frank effects were observed at the next highest dose (58.5 mg-B/kg-day).

In a continuous breeding protocol, NTP (1990b) and Fail et al. (1991) studied the reproductive toxicity of boric acid in Swiss CD-1 mice in three phases. In the cohabitation phase of this protocol, 11-week-old male and female F0 mice (40 pairs/control group and 20 pairs/dose group) were fed a diet containing 0-, 1000-, 4500-, or 9000-ppm boric acid (99% purity) for up to 27 weeks. Equivalent daily dietary doses were estimated to be 0, 26.6, 111, and 220 mg-B/kg-day for males and 0, 31.8, 152, and 257 mg-B/kg-day for females. GLP standards were followed. Following 1 week of treatment, the F0 mice were caged as breeding pairs and dosed in feed for 14 weeks. The following statistical analyses were used: (1) fertility parameters were tested using the nonparametric multiple comparison procedures of Dunn or Shirley, as modified by Williams; (2) data expressed as a proportion, such as number fertile per number cohabited, were evaluated using the Cochran-Armitage test for a dose-related trend; and (3) the Kruskal-Wallis test was used for crossover mating trials to assess equality of response among dose groups, while multiple comparison tests used the method of Dunn. The level of significance was $p < 0.05$.

In the high-dose group, impaired fertility was complete, and none of the mated pairs produced litters. The initial fertility index (percentage of cohabited pairs in at least one litter) was not statistically significantly altered in the mid-dose group, but the progressive fertility index (percentage of fertile pairs that produced four litters) was decreased relative to controls; the trend toward a lower fertility index in this group started with the first mating and progressed in severity with subsequent matings. The number of litters per pair, the number and proportion of live pups per litter, live pup body weight, and adjusted (for litter size) pup body weight also were statistically significantly lower. No effects on fertility were observed in the low-dose group relative to controls. Males were considered to be the more sensitive species. Based on fertility indices and reproductive toxicity effects, NTP (1990b; Fail et al., 1991) identified a "probable" study NOAEL for the F0 generation (cohabitation) male mice of 26 mg-B/kg-day. Based on fertility indices and reproductive toxicity effects, a reproductive LOAEL of 111 mg-B/kg-day in mice is identified for this phase of the study.

The second phase of the continuous breeding protocol involved crossover studies between control and treated mice (NTP, 1990b). These crossover studies demonstrated a reduction in fertility in mid-dose males mated to control females but not in mid-dose females mated to control males (NTP, 1990b; Fail et al., 1991). However, mid-dose females in the latter group had a longer gestational period and delivered pups with lower body weights (adjusted for litter size) than control females. Measurement of semen parameters and examination of testicular histopathology showed the following: (1) high- and mid-dose males had statistically significantly reduced testis and epididymis weights and a dose-related atrophy of seminiferous tubules; (2) mid-dose males had decreased sperm concentration, increased percentages of abnormal sperm, and other abnormalities in spermatogenic and testicular morphology; and (3) low- and mid-dose males showed statistically significant reductions in sperm motility. Due to either the absence of sperm in 12 of 15 observed males and the severe reduction in sperm counts in the other 3 males, NTP (1990b) and Fail et al. (1991) could not fully evaluate sperm motility and morphology in the high-dose group. No morphological or histopathological changes in the reproductive tract were noted in either low-dose F0 males or in treated F0 females at all doses. These data suggest a reproductive LOAEL of 26.6 mg/kg-day with no NOAEL for reduced sperm motility among male mice, and a developmental NOAEL of 31.8 mg/kg-day and LOAEL of 152 mg/kg-day among female mice for longer gestational periods and pups with lower body weights.

In the third phase of the study, NTP (1990b; Fail et al., 1991) treated F1 mice with the same doses as their parents and bred to produce the F2 generation. The high-dose F0 group did not produce any litters, and there were too few animals in the mid-dose F1 group to test the effects of treatment on F1 fertility. Therefore, only the low-dose F1 group and a group of concurrent controls were bred. In low-dose F1 animals, effects on fertility were observed relative to controls. However, increased weights of the uterus, kidney, and adrenal glands, and shortened estrus cycle lengths were observed in adult F1 females from this group. The mean F2 pup weight in the low-dose group, adjusted for litter size, was statistically significantly lower than that in the control group. Based on F1 maternal toxicity and a decrease in mean F2 pup weight, the reproductive and developmental LOAEL for this phase of the study are identified as the lowest doses tested, 26.6 and 31.8 mg-B/kg-day for males and females, respectively, with no NOAEL.

Hydrogen Chloride

No studies were identified.

Inhalation Exposure

Boron Trichloride

Stokinger and Spiegl (1953) exposed rats, mice, and guinea pigs (sex, strain, and species not specified; purity not specified; 10−15 animals/species/group) to 20-, 50-, or 85-ppm BCl_3 (4.2, 10, and 18 mg/m^3), 7 hours/day, for 1 or 2 days. Due to the hygroscopic and hydrolytic nature of this compound, the vapor decomposed into hydrolysis products immediately upon contact with air (nature of hydrolysis products not specified but presumed to include HCl) and settled as an oily liquid onto cage surfaces. Mortality was 100% at 20 and 50 ppm and 30% at 85 ppm in rats and 0% in all groups of guinea pigs. In mice, mortality was 100% in all dose groups. The study authors attributed the observed high mortality to settling of the oily decomposition products onto all cage surfaces. In a subsequent experiment, rats, mice, and guinea pigs were exposed to 20, 50, or 100 ppm for the same time period, but their cages were exchanged for clean ones every 1 to 2 hours. Mortality was significantly reduced. In rats, no mortality occurred in any dose group. In mice and guinea pigs, mortality was limited to only the high-dose group (14/15 mice and 10/10 guinea pigs). Pathological findings indicated that BCl_3 was a severe skin and respiratory irritant. Irritation occurred on those skin areas that came into direct contact with the cage surfaces, particularly the paws and mouth. The study authors concluded that BCl_3 and its hydrolysis products were highly lethal to rats and mice—but not to guinea pigs—at nominal vapor concentrations of 20 ppm (4.2 mg/m^3) or greater. However, cleaning the cages every 1 to 2 hours resulted in no mortality occurring in rats at nominal vapor concentrations of up to 100 ppm (20 mg/m^3) and in mice and guinea pigs at nominal vapor concentrations of up to 50 ppm (10 mg/m^3). This study was conducted to determine the type of personal protection respirators needed for workers involved in the production of large quantities of uranium by "special processes," of which BCl_3 and other boron halides were chemical intermediates. Exposure concentrations were considered approximate, and no measurement or characterization of the hydrolysis products was conducted. Thus, for this review, no acute quantitative values are reported.

Boric Acid and Boron Compounds

Inhalation toxicity of boron and compounds has been discussed in the IRIS toxicological review (U.S. EPA, 2004) and is summarized below.

Only one boron-oxide inhalation exposure study, which reports on exposures in rats and dogs, was available in the literature. Wilding et al. (1959) exposed a group of 70 albino rats, including both males and females, to an average concentration of 0 or 77 mg/m^3 of boron oxide aerosols (0 or 24 mg-B/m^3) 6 hours/day, 5 days/week, for 24 weeks. An additional group of four rats was exposed to 175 mg/m^3 (54 mg-B/m^3) for 12 weeks, and 10 rats were exposed to 470 mg/m^3 (146 mg-B/m^3) for 10 weeks using the same exposure regime. Three dogs (sex and breed not reported) were exposed to 57 mg/m^3 (18 mg-B/m^3) for 23 weeks. At a concentration of 470 mg/m^3, the aerosol was reported to form a dense cloud of fine particles, and the rats were covered with dust. The only clinical sign of toxicity was a slight reddish exudate from the nose of rats exposed to this concentration, which was attributed to local irritation. Body-weight gain was reduced by about 9% in the 470-mg/m^3 exposed rats, but this difference is not considered to be toxicologically significant, because body-weight decreases of less than or equal to 10% are not considered by EPA to be sufficiently large as to constitute an adverse effect (U.S. EPA, 2002). No organ effects were reported in rats exposed to 77 mg/m^3 of boron oxide aerosols (24 mg-B/m^3) for 24 weeks, although it should be noted that only limited histopathology was conducted on the testes. There was a statistically significant drop in urine pH and an increase in urine volume in rats exposed to 77 mg/m^3 (24 mg-B/m^3). Wilding et al. (1959) hypothesized that this was due to the formation of boric acid from boron oxide by hydration in the body and the diuretic properties of boron oxide. At 77 mg/m^3, a statistically significant increase in urinary creatinine also was noted. No effect on serum chemistry, hematology, organ weights, histopathology, bone strength, or liver function was reported in either rats or dogs, although not all end points were studied in all exposure groups. It is not known if this study followed GLP standards; however, it has numerous limitations in study design and reporting.

Hydrogen Chloride

IRIS (U.S. EPA, 1995) has evaluated the inhalation toxicity data for HCl, deriving a RfC of 0.02 mg/m^3 based on hyperplasia of the nasal mucosa larynx and trachea in rats (Sellakumar et al., 1985; Albert et al., 1982). The inhalation data for HCl are discussed below and summarized in Table 3.

In a 90-day inhalation study, Toxigenics (1984) exposed 31/sex/strain/species Sprague-Dawley and Fisher 344 rats and B6C3F$_1$ mice to HCl vapors of 0, 10, 20, or 50 ppm (0, 15, 30, or 75 mg/m^3, respectively) for 6 hours/day, 5 days/week, for 90 days. Mortality in rats or mice during the study was not exposure related. The only effects reported as adverse were in nasal tissues: histopathologic examination showed minimum-to-mild rhinitis and concentration- and time-dependent lesions in the anterior portion of the nasal cavity in both strains of rats in all exposed groups. In mice exposed to 50 ppm (75 mg/m^3), cheilitis and accumulation of macrophages in the peripheral tissues were observed at study termination. Eosinophilic globules in the epithelial lining of the nasal tissues were observed in mice in all exposure groups. Toxigenics (1984) did not identify a NOAEL or LOAEL for this study. However, a 6 hours/day, 5 days/week, 90-day LOAEL is identified as 15 mg/m^3 (LOAEL$_{HEC}$ = 6.1 mg/m^3) for both rats and mice, based on effects in the nasal tissues.

The chronic study by Albert et al. (1982) and Sellakumar et al. (1985) is chosen as the principal study for the derivation of the subchronic and chronic p-RfDs for boron trichloride. The study authors exposed Sprague-Dawley rats (100/sex/exposure group) to 0- (air only) and 10-ppm (15 mg/m^3) HCl vapor for 6 hours/day, 5 days/week, for a lifetime (i.e., until natural death; data were reported for up to 128 weeks). Although the study was well conducted,

compliance with GLP standards was not reported. All rats were observed daily, weighed monthly, and sacrificed at the end of the study. All rats were necropsied, with histologic sections prepared from the nasal cavities, lungs, trachea, larynx, liver, kidneys, testes, and other organs. No differences in body weights or survival were observed in rats exposed to HCl, when compared with controls. An increase in the incidence of epithelial or squamous hyperplasia in the nasal mucosa among exposed rats, compared with controls, was reported (62% in treated vs. 51% in controls; n = 99/group). Squamous metaplasia of the nasal mucosa was reported in 9% of exposed and 5% of control rats. Table B.8 presents these data. A higher rate of occurrence of hyperplasia was also reported in the laryngeal-tracheal segment of the respiratory tract (24% in exposed versus 6% in control rats (U.S. EPA, 1995). However, numerical data for this end point could not be determined because individual animal data were not available and incidence data did not distinguish between animals who had hyperplasia in both the larynx and the trachea and those with hyperplasia in either the larynx or the trachea. No squamous metaplasia in the laryngeal-tracheal segment was noted in any animals in either group. The severity of observed effects was not reported. The study authors did not identify a LOAEL or a NOAEL. However, based on the observed effects, the single dose tested, 10 ppm (15 mg/m^3; $LOAEL_{HEC}$ = 6.1 mg/m^3), is identified as a chronic LOAEL.

Reproductive and developmental studies following inhalation of HCl are limited to two studies, presented in one paper by Pavlova (1976). In the first study, two groups of 8 to 15 female rats (strain and sex not reported) were exposed to 302-ppm (450 mg/m^3) HCl for 1 hour. One group was exposed 12 days prior to mating and the other group on GD 9. In both groups, signs of severe dyspnea and cyanosis were noted, and mortality occurred in one-third of the adult rats. Fetal mortality was reported to be statistically significantly higher in pregnant rats exposed during pregnancy, likely due to maternal toxicity occurring at this exposure concentration. When the progeny were subjected to an additional exposure of 35 ppm (52 mg/m^3) at the age of 2−3 months, "functional abnormalities" in the organs of the progeny were similar to those found in the mothers. In the second study in the same paper, Pavlova (1976) exposed female rats (number and strain not reported) to 302-ppm (450 mg/m^3) HCl for 1 hour prior to mating. Exposure killed 20−30% of the rats. In rats surviving 6 days after exposure, a decrease in blood oxygen saturation was noted, and kidney, liver, and spleen damage also was reported. In addition, there were unspecified changes to the rats' estrus cycles. Appropriate controls were not utilized in these studies, and the findings were not well characterized in the publication. Therefore, neither a LOAEL nor a NOAEL for these studies is identified.

OTHER DATA

Acute Lethality Studies

Boron Trichloride

Inhalation of boron trichloride results in edema and irritation of the upper respiratory tract in humans (HSDB, 2011a). The only available data on acute inhalation of boron trichloride are lethality tests in which the LC_{50} (1-hour) for male rats was 2541 ppm (12,140 mg/m^3) (Vernot et al., 1977), and the LC_{50} (1-hour) for female rats was 21,100 mg/m^3 (HSDB, 2011a).

Boric Acid and Boron Compounds

In general, ingested boron appears to be more lethal in rats than in dogs or mice. Single-dose oral LD_{50} values for boric acid were

- 898 mg/kg (157 mg-B-kg) in an unspecified rat strain (Smyth et al., 1969)
- 600 mg/kg (105 mg-B/kg) in Sprague-Dawley rats (Weir and Fisher, 1972)
- 550 mg/kg (96 mg-B/kg) in Long-Evans rats (Weir and Fisher, 1972).

No deaths were reported in dogs exposed to a single dose of 3977 mg-Boric acid/kg (696 mg-B/kg) (Weir and Fisher, 1972). No single-dose LD_{50} studies in mice were available; however, NTP (1987) reported mortality rates of 20 and 60% in males given 14 daily doses of 12,900- or 21,000 mg-Boric acid/kg-day (2251- and 3671 mg-B/kg-day) in the diet, respectively; no mortality was observed in mice given 5300 mg/boric acid/kg-day (926 mg-B/kg-day). Treated mice were lethargic; they also exhibited discolored spleens, livers, and renal medullae, and hyperplasia and dysplasia of the forestomach (NTP, 1987).

The 4-hour LC_{50} for boric acid and other borates was greater than 2 mg-B/m^3 in rats (Hubbard, 1998). No fatalities were observed in rats exposed for 6 hours/day, 5 days/week, to 470 mg-Boron oxide/m^3 (73 mg-B/m^3) for 10 weeks, 175 mg-Boron oxide/m^3 (27 mg-B/m^3) for 12 weeks, or 77 mg-Boron oxide/m^3 (12 mg-B/m^3) for 24 weeks, or dogs exposed to 57 mg-Boron oxide/m^3 (9 mg-B/m^3) for 23 weeks (Wilding et al., 1959).

Hydrogen Chloride

Reported 30-minute LC_{50} values for HCl in rats and mice were 4701 and 2644 ppm, respectively; the LC_{50} values for 5-minute exposures were 40,989 and 13,750 ppm for rats and mice, respectively (Darmer et al., 1974). Thus, it appears that airborne HCl exposure is more lethal to mice than rats. No immediate deaths occurred among rabbits or guinea pigs exposed for 5 minutes to a concentration of 5500 mg/m^3 (3685 ppm), but 100% mortality was noted in both these animal species exposed to 1000 mg/m^3 (670 ppm) for 6 hours/day, for 5 days (WHO, 1982).

In other acute toxicity studies, delayed mortality in mice was reported to be associated with short-term exposures that did not lead to immediate death but resulted in animals dying days to several weeks following acute exposure (WHO, 1982). This mortality was attributed to the occurrence of nasal and pulmonary infections due to the disruption of normal epithelial mechanisms, which function to prevent bacterial infection and invasion in the intact animal. In support of this interpretation, focal superficial ulceration of the respiratory epithelium, at its junction with the squamous epithelium of the external nares, was reported in mice 24 hours after a single 10-minute exposure to 17 ppm (25−30 mg/m^3) (WHO, 1982).

Short-Term Exposure

Boron Trichloride

No short-term exposure studies of boron trichloride were located in the literature.

Boric Acid and Boron Compounds

Cherrington and Chernoff (2002) conducted a series of short-term mouse studies to assess the relationship between developmental toxicity and the timing of boric acid dosing during organogenesis. The findings showed that

- at oral doses of 500 and 750 mg/kg-day, the nature and extent of skeletal malformations were dose dependent;
- the most frequent malformations were of the ribs; and

- the effects of boric acid on fetal body weight and rib malformation were independent of each other and appeared to be related to the timing of the dose during the period of organogenesis (GDs 6−10).

Cherrington and Chernoff (2002) concluded that the accumulation of the adverse effect, rather than the accumulation of boric acid, was associated with the timing of the high-dose chemical insult and suggested that boric acid interfered with gastrulation and presomitic mesoderm formation under the conditions of these studies.

Hydrogen Chloride

The histopathological effects in the upper respiratory tracts of mice were studied 24 hours after a single 10-minute exposure to HCl (HSDB, 2011c). Exposure to 25 mg/m^3 (17 ppm) caused superficial ulcerations in the respiratory epithelium. Increasing the exposure to 195−417 mg/m^3 (131−280 ppm) resulted in mucosal ulceration in the adjacent respiratory epithelium and at a higher dose of 738 mg/m^3 (493 ppm); effects also were noted on the squamous epithelium of the external nares. At concentrations of 2940 mg/m^3 (1973 ppm) or more, effects were noted on parts of the squamous, respiratory, and olfactory epithelium of the upper respiratory tract. Mucosal damage also was observed.

Kaplan et al. (1988) exposed male baboons (3/group) to 0-, 500-, 5000-, or 10,000-ppm (745, 7450, and 14,900 mg/m^3, respectively) HCl for 15 minutes and observed them for 3 months. A dose-related increase in respiratory rate and minute volume immediately following exposure was observed. Decreased arterial oxygen (PO_2) was noted at the higher concentrations, but measurements at 3 days and 3 months following exposure did not show any abnormalities.

Burleigh-Flayer et al. (1985) exposed male guinea pigs via inhalation to 0-, 320-, 680-, 1040-, and 1380-ppm HCl for 1−6 minutes and measured respiratory rate and induction of sensory or pulmonary irritation. This study indicated sensory irritation at 320 ppm (477 mg/m^3) with an exposure of 6 minutes, while less severe irritation was noted at concentrations of 680 ppm (1013 mg/m^3) or higher during a 1-minute exposure. The concentration of HCl exposure was inversely related to the time of onset interval of pulmonary irritation.

Toxicokinetics

Boron Trichloride

Boron trichloride decomposes rapidly in the presence of moisture to boric acid and hydrochloric acid (U.S. EPA, 2004). Thus, oral, inhalation, or dermal exposure will result in production of these decomposition products. Toxicokinetic studies of boron trichloride have not been reported in either humans or animals. Discussion of the toxicokinetics of boron trichloride is based on its two hydrolysis products, boric acid and HCl, as follows:

$$BCl_3 + 3\ H_2O \rightarrow H_3BO_3 + 3\ HCl$$

Boric Acid and Boron Compounds

The IRIS Toxicological Profile (U.S. EPA, 2004) has discussed the toxicokinetic data for boron compounds, which are summarized below.

Boron is found in nature covalently bound to oxygen as some form of borate, such as boric acid or tetraborate. Inorganic borate compounds in the body are present as boric acid

(WHO, 1998). The boron-oxygen bonds are very strong and will not be broken except under extreme laboratory conditions. Therefore, the results of studies on the toxicity of boron and compounds generally are applicable to boric acid.

Orally ingested elemental boron also hydrolyzes into boric acid. Boric acid has been the only boron compound identified in urine following boron ingestion and has repeatedly been found to account for greater than 90% of the ingested boron dose (WHO, 1998). Studies with boron demonstrate that boric acid is well absorbed from the GI tract. In single- and repeated oral dosing studies in human volunteers, Schou et al. (1984) and Job (1973) have shown that more than 90% of boron in water was excreted in the urine over 4 days after treatment. Ingestion of boron as boric acid in food or in dietary supplements resulted in 84−90% recovery in the urine (Kent and McCance, 1941; Naghii and Samman, 1997), demonstrating that at least this percentage of the test compound was absorbed. These studies demonstrated that a high percentage of administered oral dose is absorbed in humans. In animal studies, absorption is similarly rapid and extensive, with more than 90% of orally administered boron being recovered in the urine within 1−3 days postdosing (U.S. EPA, 2004).

Boron also is well absorbed during inhalation exposure, although available data do not permit a quantitative analysis of the extent of inhalation absorption. Culver et al. (1994) showed that workers in mid- and high-exposure categories at a borax production facility had statistically significantly increased blood concentrations of boron following a work day. Due to the large size of borate dust particles in the workplace, it was unclear how much of the inhaled boron was actually absorbed through the respiratory tract. Culver et al. (1994) suggested that much of the systemic boron might have been due to absorption through the mucous membranes in the upper respiratory tract or via clearance by mucociliary activity and subsequent ingestion. Urinary boron concentrations also have been reported to be higher in rats exposed to airborne boron aerosols as compared with control rats (Wilding et al., 1959).

Boric acid has not been readily absorbed through intact skin following topical application to adult humans and newborn infants (Draize and Kelley, 1959; Friis-Hansen et al., 1982). However, Stuttgen et al. (1982) reported that boron as boric acid in an aqueous jelly vehicle has been readily absorbed through damaged skin (such as that resulting from eczema, psoriasis, and urticaria) following topical application, as evidenced by increased blood and urinary boron concentrations in these subjects. In contrast, skin-damaged individuals treated topically with boric acid in an emulsifying ointment showed no increase in urinary boron concentrations, indicating that the form of the vehicle plays a key role in the extent of dermal absorption (U.S. EPA, 2004). Nielson (1970) reported similar findings in laboratory rats.

Following absorption by either the oral or inhalation route, boric acid and other borate compounds primarily have been present in the body as undissociated boric acid. Based on data from studies in rats, boric acid uniformly distributes in soft tissues (such as liver, kidney, and muscle) outside the blood compartment, with lower concentrations found in adipose tissue and appreciably higher concentrations (i.e., close to 50%) accumulating in bone. No appreciable accumulation has been shown to occur in the testis or the epididymis of rats (U.S. EPA, 2004).

The primary route of elimination in human and rodents has been via the urine. Excretion studies have shown that greater than 90% of an orally administered dose of boric acid is rapidly excreted unchanged in the urine following treatment (Jansen et al., 1984, Schou et al., 1984).

Minor elimination pathways include feces, saliva, and sweat (Jansen et al., 1984). Studies of renal clearance (U.S. Borax, 2000; Pahl et al., 2001; Vaziri et al., 2001) showed that clearance rates of boric acid are greater in female rats than female humans and that both pregnant rats and pregnant women cleared boron somewhat more efficiently than nonpregnant rats and women. The relative rat:human clearance values were approximately 3.6:1 and 4.9:1 for pregnant and nonpregnant females, respectively, and were in close agreement with differences in kinetic parameters of approximately 4:1 predicted by allometric scaling (U.S. EPA, 2004). The variance of boron clearance in humans was slightly greater than in rats (0.35%), and the coefficient of variation (CV) was 4-fold higher in humans than in rats. However, EPA (2004) concluded, "Overall, the available pharmacokinetic data support a high degree of qualitative similarity (lack of metabolism, highly cleared through renal filtration mechanisms, and apparently consistent extravascular distribution characteristics) between the relevant experimental species and humans" (p. 29).

Hydrogen Chloride

Toxicokinetic studies have not been conducted with HCl. HCl is corrosive at high concentrations. However, at low concentrations, chloride ions are essential to normal body functions, and protons (hydrogen ions) and chloride ions are normal constituents of body fluids. Localized irritant and corrosive effects are thought to result from pH change (local deposition of H+) rather than effects of HCl, because dissociation into hydrogen and chloride ions is very rapid (HSDB, 2011c). It is generally believed that exposure to hydrogen chloride does not result in effects on organs some distance from the portal of entry (WHO, 1982).

Genotoxicity

Boron Trichloride

No studies were identified.

Boric Acid and Boron Compounds

The IRIS Toxicological Profile (U.S. EPA, 2004) discussed the genotoxicity data for boron compounds, which are summarized below.

Bacterial and mammalian cell assays have not shown evidence of boric acid mutagenicity. In *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, boric acid was not mutagenic with or without S9 metabolic activation (Benson et al., 1984; Haworth et al., 1983; NTP, 1987; Stewart, 1991). Boric acid was either not mutagenic (Iyer and Szybalski, 1958; Szybalski, 1958) or produced equivocal results (Demerec et al., 1951) in the streptomycin-dependent *Escherichia coli* Sd-4 assay. Results in mammalian mutagenicity test systems all were negative. Boric acid did not induce unscheduled DNA synthesis in primary cultures of male F344 rat hepatocytes (Bakke, 1991), forward mutations in L5178Y mouse lymphoma cells with or without S-9 activation (NTP, 1987), mutations at the thymidine kinase locus in the L5178Y mouse lymphoma cells with or without microsomal activation, or chromosome aberrations or sister chromatid exchanges in Chinese hamster ovary cells with or without S-9 metabolic activation (NTP, 1987). In a standard mouse micronucleus assay, boric acid did not induce either chromosomal or mitotic spindle abnormalities in bone marrow erythrocytes (O'Loughlin, 1991).

Hydrogen Chloride

Genotoxicity and mutagenicity test findings for HCl have been generally negative except for one study in which positive results were attributed to the contamination of the culture medium. Negative results were reported in the Ames mutagenicity test with *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, with and without metabolic activation; in a mitotic recombination assay with *Saccharomyces cerevisiae* D4, with and without metabolic activation; and in a reverse mutation test with *Escherichia coli* (HSDB, 2011c). In mammalian cell assays, HCl did not cause mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells, with or without metabolic activation. HCl was positive for chromosomal aberrations in Chinese hamster ovary cells without metabolic activation (HSDB, 2011c).

Nutrition Studies

Boron and Boron Compounds

Boron has been known, since the 1920s, to be an essential micronutrient in plants. Boron is a trace element, which is suspected to be essential in mammals, but the data are inadequate to verify this (Nielsen et al., 1987; Nielsen, 1991, 1992, 1994, 1996; Mertz, 1993; Hunt, 1994). A number of animal and human clinical studies have yielded findings supporting the nutritional essentiality of boron. Nielsen (1994) has shown that boron is needed for macromineral and cellular metabolism at the membrane level. Experimental boron nutrition research demonstrates that boron affects the metabolism or utilization of essential minerals (including calcium, magnesium, and copper), carbohydrates and fats (such as glucose and triglyceride), nitrogen, estrogen, and reactive oxygen species in a range of body tissues including blood, brain, and skeleton (Nelson, 1996). Physiological concentrations of supplemental dietary boron inhibit several enzymes involved in propagating an inflammatory response, and, thus, boron may play a role in the reduction of inflammatory disease (Hunt, 1994). Boron appears to be crucial to the utilization of calcium by bone, and supplementation with boron may arrest or reduce osteopenia and osteoporosis; Hunt (1994) has shown that boron also modulates release of insulin and metabolism of vitamin D. In human clinical studies, daily supplementation with 0.25 mg-B/day was associated with a reduction in nutritional and metabolic stress. Based on these clinical studies, Nielsen (1991) concluded that the basal requirement for boron is likely to be greater than 0.25 mg/day (0.0036 mg/kg-day).

Limited survey data indicate that the average dietary intake of boron in the United States is 0.5−3.1 mg/day (Nielsen, 1991), approximately equivalent to 0.007−0.04 mg/kg-day. Dietary boron can be obtained from consumption of fruits, vegetables, nuts, legumes, and wine. Dietary boron consumption in Europe may be higher than that in North America because of higher rates of wine consumption (ECETOC, 1995). The Institute of Medicine (IOM, 2002) has established tolerable upper intake levels (UL), but not a Recommended Dietary Intake (RDI), for boron. A UL for infants was not set. For children and adolescents aged 1−3, 4−8, 9−13 years, the ULs for boron are 3, 6, and 11 mg/day, respectively. For young adults of both genders, including pregnant and lactating females aged 14−18 years, the UL for boron is 17 mg/day. For older adults, including pregnant and lactating females aged 19−50 years, the UL for boron is 20 mg/day (IOM, 2002).

Other Toxicity Data Related to pH of Hydrogen Chloride

Chemistry Related to Hydrolysis of Boron Trichloride

Boron trichloride hydrolyzes easily in water, moist air, or ethanol to boric acid and HCl (ATSDR, 2007), as represented by the following equation.

$$BCl_3 + 3\ H_2O \rightarrow H_3BO_3 + 3\ HCl$$

Because boron trichloride rapidly and completely decomposes in water, the pH of a saturated solution is equivalent to that of concentrated hydrochloric acid. A concentrated solution of hydrochloric acid has a HCl concentration of 12.338 mol/L (Lide, 2002). This corresponds to a pH of −1.1.[3] This would require a mass of 481 g of boron trichloride to be decomposed into HCl and dissolved into water for every liter of solution.[4]

However, if boron trichloride reacts with water in an environment that is open to the atmosphere, the HCl gas produced from decomposition will not fully dissolve into solution. The amount of a gas that dissolves into a liquid solvent is directly proportional to its partial pressure above the liquid. This is demonstrated by Henry's Law given below (Zumdahl and Zumdahl, 2010):

$$P = kC$$

Where

P = Partial pressure of the gas above the solution[5]
k = Henry's law constant for the given solute/solvent combination
C = Concentration of the gas dissolved

Following entry into the upper GI tract, boron trichloride would be largely hydrolyzed.

Oral Toxicity Related to pH

The pH of the upper GI tract is about 6 and would provide considerable buffering of an ingested HCl solution. Animal studies have shown that an ingested pH in the range of approximately 2.8 to 3.5 is not likely to induce adverse effects (Clausing and Gottshalk, 1989; Upton and L'Estrange, 1977). Humans routinely and without incident consume a variety of carbonated soft drinks, energy drinks, and juices, which are acidic, with pHs as low as 2.5. Approximate beverage pHs for sample beverages include the following (Ehlen et al., 2008):

- Orange juice = 3.5
- Coca Cola® = 2.7
- Diet Coke® = 2.9
- Gatorade® = 2.8
- Red Bull® = 2.8

[3]$pH = -\log[H^+]$, Hydrogen chloride is a strong acid and fully dissociates in water, therefore, $H^+ = [HCl]$.
$pH = -\log(12.338) = -1.1$.

[4]Molar ratio given by reaction equation 3:1, $HCl:BCl_3$.
$12.338\ mol\ HCl \times \frac{1\ mol\ BCl_3}{3\ mol\ HCl} \times 117.17\ g\ BCl_3 = 481 g\ BCl_3$.

[5]The partial pressure of a gas is defined as the pressure the gas would exert if it were alone in a container (Zumdahl and Zumdahl, 2010).

Most wines have a pH between 2.9 and 3.9 (Petersen, 2010).

Additional Oral Toxicity Data for Hydrogen Chloride

Oral Exposure in Humans

In patients who survived following ingestion of highly concentrated solutions of HCl (exact concentration generally unknown), delayed gastric scarring and gastric outlet obstruction or stricture have been common. Surgical intervention and resection usually were necessary; Tucker and Gerrish (1960) reported that the major target organ of orally-ingested strong acids was the stomach, although up to 20% of cases also included the esophagus. When acids come into contact with the columnar epithelium cells of the stomach, active muscular spasms are initiated, and the acid is retained there long enough to cause burns, scarring, and other severe corrosive damage. Accidental HCl ingestion by two children produced marked strictures of the stomach, which became worse over time and necessitated surgical removal and resection (Tucker and Gerrish, 1960).

Oral Exposure in Animals

Few repeat-dose oral studies on HCl are available. The majority of these studies were conducted during and prior to the 1970s and did not conform to GLP or other national or international standards. Most reports lacked basic information such as number or strain of animals, treatment protocol and other study details, and statistical analyses, and were further limited by incomplete reporting of results, particularly pathology and histopathology. Many of the data summaries were found only in secondary documents, and original papers or reports were either unavailable or published in foreign language journals, with or without English abstracts.

Upton and L'Estrange (1977) examined the effects of dietary supplementation with hydrochloric acid on food intake and metabolism of the rat. Three experiments were conducted to observe the relationship between amount of acid added to the diet and dietary pH on a variety of blood and bone parameters in young and adult Wistar rats. When compared on the basis of amount of acid added to the diet and dietary pH, Upton and L'Estrange (1977) reported tolerance of the young and adult rats for the dietary HCl to be similar. They further concluded that the observed toxicity was due not to the strength of the acid but to the total amount added per kilogram of diet. These studies were performed to examine the physiological effects of mineral acid loading and are of interest because they address the buffering capacity of the diet relative to the acid load. For this review, the estimated daily dietary equivalents for all experiments were calculated using appropriate standard factors for body weight and food intake (U.S. EPA, 1988).

Upton and L'Estrange (1977) did not conduct pathology or histopathology of the GI tract in any of the experiments. However, these data demonstrated that dietary pHs of 3.09 to 3.5 in weanling rats and of 2.8 in adult rats had no effects on measured parameters, other than reduced plasma CO_2 or pH. Corresponding daily doses were 3.08 to 3.3 mg/kg-day for weanlings and 2.1 mg/kg-day for adults.

Clausing and Gottschalk (1989) conducted a 21-week experiment with male Wistar rats to examine a number of variables, including the effects of acidification of drinking water by hydrochloric acid. Effects of untreated tap water were compared with water acidified to either pH 3 or pH 2. Study design and the range of measured endpoints were not summarized in the abstract, and it does not appear that pathology or histopathology of the GI tract was assessed. The authors reported that acidification resulted in statistically significantly reduced proteinuria

and decreased urine volume after ingesting water with a pH of 2 and concluded that acidification of drinking water with hydrochloric acid in rodent studies should not be lower than pH 3. It is not known from the abstract whether the study followed GLP guidelines or if other effects were reported.

Acute Oral Toxicity

OECD (2002) reported acute oral LD_{50} values for HCl among female rats of 238−277 mg/kg from one 1966 German study by Hoechst (1966); however, neither clinical nor pathological observations were reported. An unpublished acute oral rat study by Monsanto (1976) gave only qualitative descriptions of GI effects without reporting the HCl concentration solutions that produced these outcomes. Effects included ulceration of stomach, acute inflammation of intestine, discoloration of the liver, and hyperemia of the lung (Monsanto, 1976). An LD_{50} for rabbits of 900 mg/kg was reported for HCl in a 1923 Monsanto study, which did not report experimental details and, thus, was given a low reliability rating by OECD (2002). The utility of this information for hazard characterization is not clear.

Peptic ulcers and esophagitis have been observed in experimental animals following acute oral treatment. Esophagitis was also observed in cats treated with hydrochloric acid (pH 1−1.3) for 1 hour (HSDB, 2011c).

Short-Term Oral Exposures

Matzner and Windwer (1937; as cited in JECFA, 1967) fed groups of 10−60 rats (strain not specified) basal diets and drinking water containing either 0.3% (3000 mg/L) hydrochloric acid; 0.3% (3000 mg/L) acid plus 20% (200,000 mg/L) pepsin; or 20% (200,000 mg/L) inactivated pepsin plus 0.1% (1000 mg/L) acid for 16 days. For this review, the estimated daily intakes of hydrochloric acid, using standard factors for body weight and food intake for adult rats of unknown strain (U.S. EPA, 1988) are calculated as 435 mg/kg-day for the 0.3% group and 145 mg/kg-day for the 0.1% group. One set of rats in each dose group was fasted for 48 hours before and allowed access to food and fluid on the third day, and this cycle was repeated five times. All groups receiving hydrochloric acid in their drinking water developed peptic ulcer-like lesions if subjected to fasting, but no lesions were seen in any of the nonfasting groups. Histologically, Matzner and Windwer (1937; as cited in JECFA, 1967) reported focal gastric submucosal edema with extension to the epithelium and muscle layer with inflammatory cellular infiltration and ulceration. This study report was not located in the open literature and, because of its age, is unlikely to have followed GLP standards. However, the gastric pathology and histology described in affected rats are similar to those described in human case reports in which concentrated solutions of hydrogen chloride are ingested either accidentally or intentionally (e.g., Tucker and Garrish, 1960; OECD, 2002).

In case reports, the pH and concentration are not generally reported. In Tucker and Garrish (1960), hydrogen chloride is described as a strong acid. Two case reports of children consuming what appears to be commercial-grade hydrogen chloride preparations are described; one child is reported as having consumed 2 ounces, whereas the quantity ingested by the other child is not given (Tucker and Garrish, 1960).

DERIVATION OF PROVISIONAL VALUES

Table 4A presents a summary of the reference values, while Table 4B shows that no cancer values are derived in this assessment for boron trichloride. **The subchronic and chronic p-RfDs for boron trichloride are based on the IRIS RfD for boron and compounds (U.S. EPA, 2004), and the subchronic and chronic p-RfCs for boron trichloride are based on the IRIS RfC for hydrogen chloride (U.S. EPA, 1995).**

Table 4A. Summary of Noncancer Reference Values for Boron Trichloride and Related IRIS Values

Toxicity Type (units)	Species/ Sex	Critical Effect[a]	p-Reference Value	POD Method[a]	POD[a]	UF_C[a]	Principal Studies[a]
BCL_3 Subchronic p-RfD (mg/kg-d)	Rat/M,F	Decreased fetal body weights	2	$BMDL_{05}$	10.3 Boron	66	Price et al., 1996a; Heindel et al., 1992
BCL_3 Chronic p-RfD (mg/kg-d)	Rat/M,F	Decreased fetal body weights	2	$BMDL_{05}$	10.3 Boron	66	Price et al., 1996a; Heindel et al., 1992
IRIS Boron RfD (mg/kg-d)	Rat/M,F	Decreased fetal body weights	2×10^{-1}	$BMDL_{05}$	10.3 Boron	66	Price et al., 1996a; Heindel et al., 1992
BCL_3 Subchronic p-RfC (mg/m^3)	Rat/M,F	Hyperplasia of nasal mucosa, trachea, and larynx	2×10^{-2}	$LOAEL_{HEC}$	6.1 HCl, chronic	300	Albert et al., 1982; Sellakumar et al., 1994
BCL_3 Chronic p-RfC (mg/m^3)	Rat/M,F	Hyperplasia of nasal mucosa, trachea, and larynx	2×10^{-2}	$LOAEL_{HEC}$	6.1 HCl, chronic	300	Albert et al., 1982; Sellakumar et al., 1994
IRIS HCL RfC (mg/m^3)	Rat/M,F	Hyperplasia of nasal mucosa, trachea, and larynx	2×10^{-2}	$LOAEL_{HEC}$	6.1 HCl, chronic	300	Albert et al., 1982; Sellakumar et al., 1994

[a]Crtical effects, POD Methods, PODs, UF_cs, and Principal Studies are those used by IRIS to derive the RfD for Boron and Compounds (U.S. EPA, 2004) or RfC for HCl (U.S. EPA, 1995).

Table 4B. Summary of Cancer Values for Boron Trichloride				
Toxicity Value	**Reference Value**	**Tumor Type or Precursor Effect**	**Species/Sex**	**Principal Study**
p-OSF	N/A			
p-IUR	N/A			

N/A = not available

DERIVATION OF SUBCHRONIC AND CHRONIC p-RfDs FOR BORON TRICHLORIDE

The subchronic and chronic p-RfDs for boron trichloride are based on the IRIS RfD for boron and compounds, with stoichiometric conversions that account for the chlorine in the BCl_3 molecule. No human or animal oral toxicity studies for oral exposure to boron trichloride are available. Table 2 summarizes potentially relevant data for boron and other boron compounds. The IRIS toxicological review (U.S. EPA, 2004) has derived a RfD of 0.2 mg/kg-day for boron and compounds, based on decreased fetal weights in rats following maternal dietary gestational exposure to boric acid (Price et al., 1996a; Heindel et al., 1992, 1994). (See Tables B.1−B.5). The data from these studies were combined for benchmark dose modeling by EPA (2004).

The RfD (U.S. EPA, 2004) for boron and compounds is based on a $BMDL_{05}$ of 59 mg-Boric acid/kg-day (10.3 mg-B/kg-day) calculated by Allen et al. (1996) from the combined data of Price et al. (1996a) and Heindel et al. (1992, 1994) for decreased fetal body weights in rats, and a composite uncertainty factor of 66. Because this POD has been used in IRIS and because available data indicate that the boric acid hydrolysis product is the likely source for potential toxicity from oral exposure to BCl_3, the IRIS RfD for boron and compounds is used in this document to derive the chronic and subchronic p-RfDs for boron trichloride.

To account for molecular weight, the RfD of 0.2 mg/kg-day for boron is adjusted using the boron trichloride-to-boron molecular weight ratio of 117.17 g BCl_3/mol/10.81 g-B/mol = 10.84. Therefore, a chronic p-RfD for boron trichloride, based on the RfD for boron and compounds is derived as follows:

$$\begin{aligned}\textbf{Chronic p-RfD}_{\text{Boron Trichloride}} &= \text{IRIS RfD}_{\text{boron}} \times (\text{MW}_{\text{boron trichloride}} \div \text{MW}_{\text{boron}}) \div \text{UF}_{\text{D}} \\ &= 0.2 \text{ mg-B/kg-day} \times (117.17 \text{ g } BCl_3\text{/mol} \div 10.81 \text{ g-B/mol}) \\ &= 0.2 \text{ mg-B/kg-day} \times 10.84 \\ &= \textbf{2 mg/kg-day}\end{aligned}$$

In the absence of subchronic data, the IRIS RfD for boron, is also adopted as the subchronic p-RfD for boron trichloride after stoichiometric conversion.

As the p-RfDs for boron trichloride are derived explicitly from the IRIS RfD for boron, the uncertainties associated with the point of departure (POD) for boron, as well as confidence in the principal study and database for boron, all contribute to uncertainty for boron trichloride. Confidence in the boron study, database, and RfD are all high. According to EPA (2004):

Confidence in the principal developmental studies is high; they are well-designed studies that examined relevant developmental endpoints using a large number of animals. Similar developmental effects were noted in rats, mice, and rabbits. Confidence in the data base is high due to the existence of several subchronic and chronic studies, as well as adequate reproductive and developmental toxicology data. High confidence in the RfD follows.

For boron trichloride, there is additional potential uncertainty due to the contribution to oral toxicity from the second hydrolysis breakdown product, HCl. However, what is known about the toxicokinetics and potential for systemic oral toxicity of HCl does not suggest that HCl is likely to have an additive or synergistic effect on developmental toxicity, the critical end point for derivation of the boron RfD. In addition, point-of-entry effects are unlikely from contact with the HCl hydrolyzed from a 2-liter solution of the adult daily dose of boron trichloride at the p-RfD. Therefore, the overall confidence in the chronic and subchronic p-RfDs for boron trichloride, based on the boron RfD, is high (see Table 5).

Table 5. Confidence Descriptor for Subchronic and Chronic p-RfDs for Boron Trichloride

Confidence Categories	Designation[a]	Discussion
Confidence in Study	H	Confidence in the principal developmental studies for boron is high: they are well-designed studies that examined developmental end points of boron using a large number of animals. Similar developmental effects were noted in rats, mice, and rabbits.
Confidence in Database	H	Confidence in the database for boron is high due to the existence of several subchronic and chronic studies, as well as adequate reproductive and developmental toxicology data for boron. It is unlikely that hydrogen chloride hydrolyzed from boron trichloride has an additive or synergistic effect on developmental toxicity.
Confidence in Chronic p-RfD[b]	H	The overall confidence in the p-RfD is high.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

DERIVATION OF SUBCHRONIC AND CHRONIC p-RfCs FOR BORON TRICHLORIDE

The subchronic and chronic p-RfCs for boron trichloride are based on the IRIS RfC for hydrogen chloride (U.S. EPA, 1995). With the exception of the acute animal studies by Stokinger and Spiegl (1953) and Vernot (1977), no human or animal inhalation toxicity studies of boron trichloride are available.

Table 2 summarizes potentially relevant inhalation data for boron compounds. Epidemiologic studies in the workplace have reported respiratory and nasal tract irritation from inhalation exposure to high concentrations of boron compounds. Epidemiologic studies do not provide evidence for boron-induced human reproductive toxicity. The only available repeated exposure inhalation toxicity animal study for boron compounds is Wilding et al. (1959), in which albino rats and dogs were exposed to boron oxide aerosols at various concentrations for various

exposure durations. Minimal eye irritant effects at the highest concentration tested, 470 mg/m^3, were attributed to direct ocular contact with billowing dust particles. No histopathology was observed in the testes, although only limited microscopic examinations were conducted.

Table 3 summarizes potentially relevant inhalation data for hydrogen chloride, the other hydrolysis product of boron trichloride. It is well established that boron trichloride immediately hydrolyzes to boric acid and HCl when exposed to water or water vapor (U.S. EPA, 2000; ATSDR, 2007). Human and animal data have shown that the adverse effects of inhalation exposure to HCl occur primarily in the upper respiratory tract, and to a lesser extent, further along the portal of entry for inhalation (WHO, 1982). Localized irritant and corrosive effects are thought to result from pH change (local deposition of H+) rather than hydrogen chloride, per se, because dissociation into hydrogen and chloride ions is very rapid (HSDB, 2011c).

IRIS (U.S. EPA, 1995) derived a chronic RfC of 0.02 mg/m^3 for HCl, based on a chronic rat LOAEL of 15 mg/m^3 (Albert et al., 1982; Sellakumar et al., 1985) for hyperplasia of the nasal mucosa, trachea, and larynx. IRIS (U.S. EPA, 1995) calculated a $LOAEL_{ADJ}$ of 2.5 mg/m^3, and a $LOAEL_{HEC}$ for a gas:respiratory effect in the extrathoracic and tracheobronchial regions of 6.1 mg/m^3, and applied a composite uncertainty factor of 300.

To account for molecular weight, the HCl RfC of 0.02 mg/m^3 is adjusted using the boron trichloride-to-HCl molecular weight ratio of [117.17 g BCl_3/mol]/[36.46 g HCl/mol] and the 3:1 molecular hydrolysis ratio. Because each molecule of boron trichloride hydrolyzes to three molecules of hydrogen chloride, the chronic p-RfC for boron trichloride is calculated from the IRIS RfC for HCl, as follows:

$$\begin{aligned}\textbf{Chronic p-RfC} &= \text{IRIS RfC}_{HCl} \times (MW_{\text{boron trichloride}} \div [3 \times MW_{HCl}]) \\ &= 0.02 \text{ mg HCl/m}^3 \times (117.17 \text{ g-BCl}_3\text{/mol} \div \\ &\quad [3 \times 36.46 \text{ g HCl/mol}]) \\ &= 0.02 \text{ mg HCl/m}^3 \times 1.07 \text{ BCl}_3\text{/HCl} \\ &= \mathbf{2 \times 10^{-2} \text{ mg/m}^3 \text{ boron trichloride}}\end{aligned}$$

In the absence of data for effects of subchronic-duration inhalation exposure to HCl, the **subchronic p-RfC** for boron trichloride also is derived from the chronic data and is the same as the chronic p-RfC of **2×10^{-2} mg/m^3**.

The uncertainties associated with the POD for HCl, as well as confidence in the principal study, database, and RfC for HCl all contribute to the uncertainty for boron trichloride. According to EPA (1995):

> *The chronic study used only one dose and limited toxicological measurements. The supporting data consist of two subchronic bioassays; the database does not provide any additional chronic or reproductive studies. Therefore, low confidence was recommended for the study, database, and the RfC.*

Therefore, the overall confidence in the chronic p-RfC for boron trichloride is based on the HCl database confidence of low. For boron trichloride, there is additional uncertainty due to the potential contribution to inhalation toxicity from the other hydrolysis breakdown product, boric acid. What is known about the toxicokinetics and the potential for portal-of-entry

inhalation toxicity of boron suggests that boron may also contribute in an additive or synergistic way to the irritant and corrosive mucosal effects induced by HCl. However, the contributions of the boric acid hydrolysis product to the portal-of-entry inhalation effects of HCl are likely to be small. See Table 6 for the confidence descriptors for the chronic p-RfC for boron trichloride.

Table 6. Confidence Descriptor for Chronic p-RfC for Boron Trichloride

Confidence Categories	Designation[a]	Discussion
Confidence in Study	L	Confidence in the principal study for HCl is low because it used only one dose and had limited toxicological measurements.
Confidence in Database	L	Confidence in the database is low due to only two subchronic studies on HCl. Reproductive and developmental studies following inhalation of HCl are limited to two poorly reported animal studies. Contributions of boric acid to the portal-of-entry inhalation effects of HCl are likely to be small.
Confidence in Chronic p-RfC[b]	L	The overall confidence in the p-RfC is low.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR BORON TRICHLORIDE

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR (WOE)

No human or animal data are available to inform a carcinogenicity assessment of boron trichloride. The database for boron trichloride does not include human epidemiologic studies or subchronic or chronic animal bioassays. However, boron trichloride is rapidly hydrolyzed to boric acid and HCl; the carcinogenic potential of boron trichloride is likely to be similar to that of either of these two substances. IRIS (U.S. EPA, 2004) has described the carcinogenicity data of boron and boron compounds as being *"Inadequate for an Assessment of the Human Carcinogenic Potential,"* using guidelines equivalent to those in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), and no newer carcinogenicity data are available. No human or animal data are available on the carcinogenicity of HCl. The EPA has not classified HCl for carcinogenicity. IARC has classified HCl in Group 3, *Inadequate Evidence for Carcinogenicity in Humans and in Experimental Animals* (IARC, 1992). Thus, the provisional carcinogenicity descriptor for exposure to boron trichloride is *"Inadequate Information to Assess Carcinogenic Potential"* (see Table 7).

Table 7. Cancer WOE Descriptor for Boron Trichloride			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available for boron trichloride or for its hydrolysis products, boric acid and hydrogen chloride.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	No strong animal cancer data are available, and no weaker human and animal data are available for boron trichloride or for its hydrolysis products, boric acid and hydrogen chloride.
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	No carcinogenicity data are available for boron trichloride or its hydrolysis products.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**U.S. EPA (2004) has used this WOE descriptor for the carcinogenicity data on boron and boron compounds; IARC (1992) used a similar WOE descriptor for the carcinogenic potential of hydrogen chloride.**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	No data are available that suggest boron trichloride or its hydrolysis products do not have carcinogenic potential.

PROVISIONAL ORAL SLOPE FACTOR (p-OSF) DERIVATION

No p-OSF can be derived due to a lack of carcinogenicity data.

PROVISIONAL INHALATION UNIT RISK (p-IUR) DERIVATION

No p-IUR can be derived due to a lack of carcinogenicity data.

APPENDIX A. PROVISIONAL SCREENING VALUES

Appendix A is not applicable.

APPENDIX B. RELEVANT DATA TABLES

Table B.1. Maternal Toxicity in CD-1 Rats Exposed to Dietary Boric Acid on GDs 6−15 and GDs 0−20[a]

Doses	Boric Acid as mg-B/kg-day, GDs 0−20				Boric Acid as mg-B/kg-day, GDs 6−15	
	0	**13.6**	**28.5**	**57.7**	**0**	**94.2**
No. dams treated (pregnant at sacrifice)	29 (28)	29 (28)	29 (26)	29 (26)	14 (14)	14 (14)
Maternal weight gain (g)[b]						
Gestation (GDs 0−20)	160.6 ± 0.8**	157.5 ± 3.0	156.6 ± 3.6	143.6 ± 3.9*	157.8 ± 6.1	102.5 ± 5.3*
Treatment (GDs 6−15)					54.0 ± 2.9	22.9 ± 3.1*
Corrected weight gain[c]	71.2 ± 2.9**	72.1 ± 2.1	74.6 ± 3.1	81.4 ± 2.5*	66.6 ± 4.8	66.2 ± 6.2
Gravid uterine weight	88.4 ± 2.6**	85.3 ± 2.1	82.0 ± 2.0	62.1 ± 3.1*	88.9 ± 3.6	36.2 ± 4.4*
Maternal body weight (g)[b] on GD 20	409 ± 5	405 ± 4	404 ± 4	393 ± 5	417 ± 6	364 ± 5*
Maternal liver weight[b]						
Absolute (g)	17.15 ± 0.25	17.59 ± 0.27	17.86 ± 0.30	17.54 ± 0.35	17.27 ± 0.40	17.12 ± 0.59
Relative (% body weight)	4.20 ± 0.05**	4.35 ± 0.06	4.42 ± 0.07*	4.46 ± 0.07*	4.15 ± 0.07	4.70 ± 0.13*
Maternal right kidney weight[b]						
Absolute (g)[b]	1.23 ± 0.02**	1.25 ± 0.02	1.35 ± 0.06	1.32 ± 0.03	1.21 ± 0.03	1.37 ± 0.04*
Relative (% body weight)	0.302 ± 0.006**	0.309 ± 0.006	0.335 ± 0.016*	0.338 ± 0.007*	0.289 ± 0.009	0.376 ± 0.009*

[a]NTP (1990a); Heindel (1992).
[b]Includes all dams pregnant at sacrifice; mean ± standard error of the mean (SEM).
[c]Gestational weight gain minus gravid uterine weight.

*$p < 0.05$ by pair-wise comparison to the control group.
**$p < 0.05$, test for linear trend.

Table B.2. Developmental Toxicity in CD Rats following Maternal Exposure to Dietary Boric Acid on GDs 0−20 or 6−15[a]

Doses	Boric Acid as mg-B/kg-day, GDs 0−20				Boric Acid as mg-B/kg-day, GDs 6−15	
	0	**13.6**	**28.5**	**57.7**	**0**	**94.2**
All pregnant dams[b]	28	28	26	26	14	14
Number of implantation sites/litter[c]	15.9 ± 0.3	16.4 ± 0.4	16.2 ± 0.3	16.1 ± 0.4	16.0 ± 0.5	15.8 ± 0.5
Resorptions/litter[c]	3.5 ± 1.0	5.9 ± 1.2	3.4 ± 0.8	8.6 ± 3.9	4.4 ± 1.9	36.2 ± 8.7*
% Litters with one or more resorptions	39	61	46	46	36	100
% Late fetal deaths/litter[c,d]	0.0 ± 0.0	0.3 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.4 ± 1.6*
% Litters with one or more late fetal deaths	0	4	0	0	0	21
% Adversely affected implants/litter[c,d]	5.46 ± 1.35**	8.66 ± 1.90	11.17 ± 2.16*	53.58 ± 5.63*	7.06 ± 2.41	77.71 ± 6.77*
% Litters with one or more adversely affected implants[d]	50**	75*	85*	100*	50	100*
Dams with live litters[e]	28	28	26	25	14	14
Number of live fetuses/litter[c]	15.4 ± 0.4	15.4 ± 0.5	15.7 ± 0.4	15.4 ± 0.5	15.4 ± 0.7	9.7 ± 1.6*
Average fetal body weight (g)/litter[c]						
Male fetuses	3.779 ± 0.061**	3.554 ± 0.051*	3.280 ± 0.053*	2.405 ± 0.059*	3.820 ± 0.068	1.778 ± 0.153*
Female fetuses	3.609 ± 0.059**	3.364 ± 0.046*	3.130 ± 0.050*	2.266 ± 0.046*	3.646 ± 0.064	1.814 ± 0.060*
% Malformed fetuses/litter[c,f]	2.1 ± 0.8**	2.6 ± 1.4	7.8 ± 2.4*	50.2 ± 5.4*	2.8 ± 1.4	72.6 ± 8.1*
% Litters with one or more malformed fetuses						
All malformations	21**	21	50*	100*	29	100*
Gross malformations	4	0	4	4	7	71*
Visceral malformations	7	4	0	36*	14	86*
Skeletal malformations	14**	18	46*	100*	14	100*
% Fetuses/litter with variations[c,f]	21.2 ± 3.2	7.7 ± 1.4*	8.8 ± 1.9*	27.2 ± 4.4	24.2 ± 4.9	59.5 ± 6.8*
% Litters with variations	96	71*	58*	92	93	100

[a]NTP (1990a); Heindel (1992).
[b]Includes all dams pregnant at sacrifice; litter size = number of implantation sites per dam.
[c]Reported as mean ± standard error of the mean (SEM).
[d]Adversely affected implants = nonlive implants plus malformed fetuses.
[e]Includes only dams with live fetuses; litter size = number of live fetuses per dam.
[f]Only live fetuses were examined for malformations and variations.

*$p < 0.05$ by pair-wise comparison to the control group.
**$p < 0.05$, test for linear trend or test for linear trend on proportions.

Table B.3. Maternal Toxicity in CD Rats Exposed to Dietary Boric Acid on GDs 0−20 in Phase I (Teratology) Study and on PNDs 0−20 in Phase II (Postnatal) Studies[a]

Doses[b]	**Boric Acid as mg-B/kg-day**					
Phase I	**0**	**3.3**	**6.3**	**9.3**	**13.3**	**25.0**
Phase II	**0**	**3.2**	**6.5**	**9.7**	**12.9**	**25.3**
Dams treated (per study phase)	28−34	28−34	28−34	28−34	28−34	29−34
Dams removed (Total)[c]	1	0	0	0	1	1
Dams pregnant (%)						
Phase I (Teratology)	27 (96)	29 (91)	27 (96)	29 (100)	30 (97)	27 (90)
Phase II (Postnatal)	29 (94)	29 (96)	28 (88)	27 (94)	25 (89)	28 (97)
Selected Maternal Weight Changes (g)[d,e]						
Phase I (Gestation; GDs 0−20)[f]	150 ± 5	157 ± 4	153 ± 4	146 ± 5	150 ± 4	140 ± 5
Phase I (Gravid uterine weight)	88 ± 4	90 ± 3[§]	91 ± 3	85 ± 4	86 ± 4	79 ± 3
Selected Maternal Organ Weights[d,e]						
Relative right kidney weight (g) (% body weight)[g]						
Phase I (GD 20)	0.29 ± 0.01	0.31 ± 0.01[§]	0.29 ± 0.01	0.30 ± 0.01	0.30 ± 0.01	0.32 ± 0.01*
Phase II (PND 21)	0.46 ± 0.01	0.46 ± 0.01	0.47 ± 0.01	0.49 ± 0.02	0.45 ± 0.01	0.48 ± 0.01

[a]NTP, (1994); Price et al., (1996a).
[b]Phase I, teratologic evaluation; Phase II, postnatal evaluation.
[c]Each dam was removed for one of the following reasons: PND 0 not determined (Phase II), early delivery of a litter (Phase I), or sipper tube malfunction (Phase I). No dam was euthanized or sacrificed *in extremis* prior to study termination.
[d]Mean ± standard error of the mean (SEM).
[e]Only maternal body and organ (absolute and relative liver and kidney) weight changes that were statistically significant by pair-wise comparison to concurrent vehicle control ($p < 0.05$) or those which showed a statistically significant linear trend ($p < 0.05$) are reported in this table. No maternal effects were observed for any parameters during Phase II at any dose.
[f]Weight gain during gestation minus gravid uterine weight.
[g]Kidney weight ÷ body weight

[§]$p < 0.05$; test for linear trend.
*$p < 0.05$; Dunnett's test or Williams' test; pair-wise comparison to the concurrent vehicle control group.

Table B.4. Selected Developmental Toxicity Parameters in CD Rats following Maternal Exposure to Boric Acid in Feed on GDs 0−20 for Phase I (Teratology Study) and on PNDs 0−21 for Phase II (Postnatal Study)[a]

Doses[b]	**Boric Acid as mg-B/kg-day**					
Phase I	**0**	**3.3**	**6.3**	**9.3**	**13.3**	**25.0**
Phase II	**0**	**3.2**	**6.5**	**9.7**	**12.9**	**25.3**
Dams (%) delivering litters[c,d]						
GD ≤ 22	26(90)	22 (81)[§]	22(79)	25(86)	16(64)	19(68)
GD 23	3(10)	5(10)	6(21)	4(14)	9(36)	9(32)
Resorptions/litter on GD 20[e]	9.5 ± 3.6	3.3 ± 10	2.6 ± 0.8	3.9 ± 0.8	6.7 ± 3.4	4.8 ± 1.1
% Litters with one or more resorptions on GD 20	70	34*	53	32*	37*	48
Postnatal mortality/litter[e]						
PNDs 0−4[§]	0.55 ± 0.31	1.17 ± 0.49[§]	1.80 ± 1.02	1.35 ± 0.51	1.83 ± 0.71	2.80 ± 0.76
PNDs 4−21	0.76 ± 0.45	1.14 ± 0.47	0.84 ± 0.49	0.38 ± 0.27	1.00 ± 0.48	0.45 ± 0.31
PNDs 0−20[§]	0.93 ± 0.39	2.28 ± 0.74[§]	2.64 ± 1.08	2.08 ± 0.72	2.83 ± 0.77	3.25 ± 0.76
Live litters						
GD 20	26	29	27	29	29	27
PND 21	29	27	27	29	25	27
Average fetal or pup weights in grams per-litter[c]						
Male fetuses or pups						
GD 20	3.71 ± 0.05	3.64 ± 0.05[§]	3.62 ± 0.05	3.60 ± 0.07	3.48 ± 0.05*	3.23 ± 0.06*
PND 0	6.61 ± 0.10	6.79 ± 0.13	6.68 ± 0.13	6.53 ± 0.11	6.49 ± 0.13	6.59 ± 0.11
PND 21	43.25 ± 1.71	47.82 ± 1.91	44.29 ± 1.70	41.99±1.39	43.76 ± 1.16	42.56 ± 1.19
Female fetuses or pups[e]						
GD 20	3.52 ± 0.05	3.47 ± 0.04[§]	3.45 ± 0.06	3.38 ± 0.06	3.27 ± 0.05*	3.04 ± 0.05*
PND 0	6.21 ± 0.11	6.34 ± 0.09	6.26 ± 0.15	6.18 ± 0.10	6.29 ± 0.16	6.20 ± 0.10
PND 21	41.22 ± 1.61	44.88 ± 1.57	42.20 ± 1.77	40.27 ± 1.21	43.94 ± 1.84	40.45 ± 1.09
Offspring with skeletal malformations and variations						
% Offspring/litter with skeletal malformations[e]						
GD 20[§]	2.0 ± 0.7	0.9 ± 0.6[§]	1.6 ± 0.6	2.5 ± 0.7	3.5 ± 1.2	4.3 ± 1.5
PND 21[§]	0.0 ± 0.0	2.0 ± 0.8*[§]	0.6 ± 0.6	0.2 ± 0.2	1.3 ± 0.8	3.9 ± 1.8*
% Litters with skeletal malformations[f]						
GD 20	27	10	22	34	31	30
PND 21	0	22*	4	3	12	22*
% Offspring/litter with skeletal variations[e,f]						
GD 20	10.0 ± 2.0	3.4 ± 1.0	6.5 ± 1.8	5.3 ± 1.4	7.4 ± 2.1	12.1 ± 3.0
PND 21	6.8 ± 1.9	9.6 ± 2.4	4.9 ± 1.3	4.9 ± 1.5	4.4 ± 1.6	4.8 ± 1.9

Table B.4. Selected Developmental Toxicity Parameters in CD Rats following Maternal Exposure to Boric Acid in Feed on GDs 0−20 for Phase I (Teratology Study) and on PNDs 0−21 for Phase II (Postnatal Study)[a]

Doses[b]	**Boric Acid as mg-B/kg-day**					
Phase I	**0**	**3.3**	**6.3**	**9.3**	**13.3**	**25.0**
Phase II	**0**	**3.2**	**6.5**	**9.7**	**12.9**	**25.3**
% Litters with skeletal variations[f]						
GD 20	60	34	52	41	55	63
PND 21	41	52	44	34	36	33
% Offspring/litter with short rib XIII[e,f]						
GD 20	0.0 ± 0.0	0.0 ± 0.0[§]	0.2 ± 0.2	0.6 ± 0.5	1.4 ± 0.7*	3.2 ± 1.2*
PND 21	0.0 ± 0.0	1.5 ± 0.6[§]	0.6 ± 0.6	0.2 ± 0.2	0.6 ± 0.5	3.9 ± 1.8*
% Litters with short rib XIII[f]						
GD 20	0	0	4	7	14	22*
PND 21	0	19	4	3	8	22*
% Offspring/litter with wavy rib[e,f]						
GD 20	0.0 ± 0.0	0.3 ± 0.3[§]	0.0 ± 0.0	0.8 ± 0.7	2.1 ± 0.9*	9.9 ± 3.0*
PND 21	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.3	0.2 ± 0.2	0.0 ± 0.0	0.0 ± 0.0
% Litters with wavy rib[f]						
GD 20	0	3[§]	0	7	21*	48*
PND 21	0	0	4	3	0	0

[a]NTP (1994); Price et al. (1996a).
[b]Phase I, teratologic evaluation; Phase II, postnatal evaluation.
[c]Includes all dams in Phase II that delivered a litter.
[d]The overall χ^2 test for differences among groups for GDs 21, 22, and 23 was not statistically significant ($p = 0.315$). When the proportions were expressed as ≤GD 22 vs. GD 23, the overall χ^2 test also was not statistically significant ($p = 0.144$), but the Cochran-Armitage Trend Test was $p = 0.02$.
[e]Mean ± standard error of the mean (SEM).
[f]Classification of skeletal findings as malformations or variations is in accordance with study authors' and NTP (1994) classifications. In this study, short rib XIII is considered to be a malformation (although others consider it to be a variant). Wavy rib is considered to be a skeletal variant. These two skeletal end points were the only ones that were statistically significant ($p < 0.05$, relative to concurrent controls, at higher doses.)

[§]$p < 0.05$; test for linear trend or Cochran-Armitage trend test.
*$p < 0.05$; Dunnett's test, Williams' test, or Fisher's Exact test pair-wise comparison to the concurrent vehicle control group.

Table B.5. Selected Developmental Toxicity Parameters in CD Rats following Maternal Exposure to Boric Acid in Feed on GDs 0 to 20 for Phase I (Teratology Study) and on PNDs 0−21 for Phase II (Postnatal Study)[a]

Doses[b]	Boric Acid as mg-B/kg-day					
Phase I	**0**	**3.3**	**6.3**	**9.3**	**13.3**	**25**
Phase II	**0**	**3.2**	**6.5**	**9.7**	**12.9**	**25.3**
Dams (%) delivering litters[c,d]						
GD ≤ 22	26(90)	22 (81) [§]	22(79)	25(86)	16(64)	19(68)
GD 23	3(10)	5(10)	6(21)	4(14)	9(36)	9(32)
Resorptions/litter on GD 20[e]	9.5 ± 3.6	3.3 ± 10	2.6 ± 0.8	3.9 ± 0.8	6.7 ± 3.4	4.8 ± 1.1
% Litters with one or more resorptions on GD 20	70	34*	53	32*	37*	48
Postnatal mortality/litter[e]						
PNDs 0−4	0.55 ± 0.31	1.17 ± 0.49[§]	1.80 ± 1.02	1.35 ± 0.51	1.83 ± 0.71	2.80 ± 0.76
PNDs 4−21	0.76 ± 0.45	1.14 ± 0.47	0.84 ± 0.49	0.38 ± 0.27	1.00 ± 0.48	0.45 ± 0.31
PNDs 0−21	0.93 ± 0.39	2.28 ± 0.74[§]	2.64 ± 1.08	2.08 ± 0.72	2.83 ± 0.77	3.25 ± 0.76
Live litters						
GD 20	26	29	27	29	29	27
PND 21	29	27	27	29	25	27
Average fetal or pup weight (g) on a per-litter[c]						
Male fetuses or pups[e]						
GD 20	3.71 ± 0.05	3.64 ± 0.05[§]	3.62 ± 0.05	3.60 ± 0.07	3.48 ± 0.05*	3.23 ± 0.06*
PND 0	6.61 ± 0.10	6.79 ± 0.13	6.68 ± 0.13	6.53 ± 0.11	6.49 ± 0.13	6.59 ± 0.11
PND 21	43.25 ± 1.71	47.82 ± 1.91	44.29 ± 1.70	41.99 ± 1.39	43.76 ± 1.16	42.56 ± 1.19
Female fetuses or pups[e]						
GD 20	3.52 ± 0.05	3.47 ± 0.04[§]	3.45 ± 0.06	3.38 ± 0.06	3.27 ± 0.05*	3.04 ± 0.05*
PND 0	6.21 ± 0.11	6.34 ± 0.09	6.26 ± 0.15	6.18 ± 0.10	6.29 ± 0.16	6.20 ± 0.10
PND 21	41.22 ± 1.61	44.88 ± 1.57	42.20 ± 1.77	40.27 ± 1.21	43.94 ± 1.84	40.45 ± 1.09
Summary of offspring/litter with skeletal malformations and variations						
% Offspring/litter with skeletal malformations[e]						
GD 20	2.0 ± 0.7	0.9 ± 0.6[§]	1.6 ± 0.6	2.5 ± 0.7	3.5 ± 1.2	4.3 ± 1.5
PND 21	0.0 ± 0.0	2.0 ± 0.8*[§]	0.6 ± 0.6	0.2 ± 0.2	1.3 ± 0.8	3.9 ± 1.8*
% Litters with skeletal malformations						
GD 20	27	10	22	34	31	30
PND 21	0	22*	4	3	12	22*
% Offspring/litter with short rib XII[e,f]						

Table B.5. Selected Developmental Toxicity Parameters in CD Rats following Maternal Exposure to Boric Acid in Feed on GDs 0 to 20 for Phase I (Teratology Study) and on PNDs 0−21 for Phase II (Postnatal Study)[a]

Doses[b]	Boric Acid as mg-B/kg-day					
Phase I	**0**	**3.3**	**6.3**	**9.3**	**13.3**	**25**
Phase II	**0**	**3.2**	**6.5**	**9.7**	**12.9**	**25.3**
GD 20	0.0 ± 0.0	0.0 ± 0.0[§]	0.2 ± 0.2	0.6 ± 0.5	1.4 ± 0.7*	3.2 ± 1.2*
PND 21	0.0 ± 0.0	1.5 ± 0.6[§]	0.6 ± 0.6	0.2 ± 0.2	0.6 ± 0.5	3.9 ± 1.8*
% Litters with short rib XIII[f]						
GD 20	0	0[§]	4	7	14	22*
PND 21	0	19	4	3	8	22*
% Litters with skeletal variations						
GD 20	60	34	52	41	55	63
PND 21	41	52	44	34	36	33
% Offspring/litter with skeletal variations[e,f]						
GD 20	10.0 ± 2.0	3.4 ± 1.0	6.5 ± 1.8	5.3 ± 1.4	7.4 ± 2.1	12.1 ± 3.0
PND 21	6.8 ± 1.9	9.6 ± 2.4	4.9 ± 1.3	4.9 ± 1.5	4.4 ± 1.6	4.8 ± 1.9
% Litters with wavy rib[f]						
GD 20	0	3[§]	0	7	21*	48*
PND 21	0	0	4	3	0	0
% Offspring/litter with wavy rib[e,f]						
GD 20	0.0 ± 0.0	0.3 ± 0.3[§]	0.0 ± 0.0	0.8 ± 0.7	2.1 ± 0.9*	9.9 ± 3.0*
PND 21	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.3	0.2 ± 0.2	0.0 ± 0.0	0.0 ± 0.0

[a]NTP (1994); Price et al. (1996a).
[b]Phase I, teratologic evaluation; Phase II, postnatal evaluation.
[c]Includes all dams in Phase II that delivered a litter.
[d]The overall χ^2 test for differences among groups for GDs 21, 22, and 23 was not statistically significant ($p = 0.315$). When the proportions were expressed as ≤GD 22 vs. GD 23, the overall χ^2 test also was not statistically significant ($p = 0.144$), but the Cochran-Armitage Trend Test was $p = 0.02$.
[e]Mean ± standard error of the mean (SEM).
[f]Classification of skeletal findings as malformations or variations is in accordance with study authors' and NTP (1994) classifications. In this study, short rib XIII is considered to be a malformation (although others consider it to be a variant). Wavy rib is considered to be a skeletal variant. These two skeletal end points were the only ones that were statistically significant ($p < 0.05$, relative to concurrent controls, at higher doses).

[§]$p < 0.05$; test for linear trend or Cochran-Armitage trend test.
*$p < 0.05$; Dunnett's test, Williams' test, or Fisher's Exact test pair-wise comparison to the concurrent vehicle control group.

Table B.6. Selected Maternal Toxicity Parameters Following Exposure of CD-1 Mice to Boric Acid in Feed on GDs 0−17[a]

Doses	Boric Acid as mg-B/kg-day			
	0	**43.4**	**79.0**	**175.3**
No. dams treated (pregnant at sacrifice)	29 (27)	28 (27)	29 (27)	28 (26)
Maternal weight gain (g)[b]				
Gestation/treatment period	21.4±0.8[§]	21.7 ± 0.5	21.1 ± 0.7	16.0 ± 1.1*
Corrected weight gain[c]	4.5 ± 0.3	5.6 ± 0.3	4.9 ± 0.4	4.7 ± 0.5
Gravid uterine weight (g)	16.9 ± 0.7[§]	16.1 ± 0.5	16.1 ± 0.6	12.1 ± 0.6*
Maternal body weight (g) on GD 17	49.3 ± 1.1[§]	48.3 ± 0.8	49.0 ± 1.0	43.1 ± 1.1*
Maternal liver weight[b]				
Absolute (g)	2.36 ± 0.04[§]	2.36 ± 0.04	2.38 ± 0.05	2.15 ± 0.06*
Relative (% body weight)	4.95 ± 0.08	5.02 ± 0.07	5.00 ± 0.09	5.13 ± 0.07
Maternal right kidney weight[b]				
Absolute (g)	0.20 ± 0.01[§]	0.19 ± 0.01	0.21 ± 0.01	0.22 ± 0.01
Relative (% body weight)	0.41 ± 0.02[§]	0.41 ± 0.02	0.45 ± 0.02	0.54 ± 0.04*
Renal histopathology				
Renal tubular dilation and/or regeneration[d]	0/10	2/10	8/10	10/10

[a]NTP (1990a); Heindel et al. (1992).
[b]Includes all dams pregnant at sacrifice, mean ± standard error of the mean (SEM).
[c]Gestational weight gain minus gravid uterine weight.
[d]Number affected/number examined.

*$p < 0.05$ by pairwise comparison to the control group.
[§]$p < 0.05$, test for linear trend.

Table B.7. Selected Developmental Toxicity Parameters following Maternal Exposure of CD-1 Mice to Boric Acid in Feed on GDs 0−17[a]

Doses	Boric Acid as mg-B/kg-day			
	0	**43.4**	**79.0**	**175.3**
All litters[b]	27	27	27	26
Number of implantation sites/litter[c]	12.4 ± 0.6	12.0 ± 0.4	12.1 ± 0.4	12.1 ± 0.5
% Resorptions/litter[c]	6.1 ± 1.6[§]	6.2 ± 1.3	4.8 ± 1.4	19.3 ± 4.5*
% Litters with one or more resorptions[c]	44	56	37	73*
% Late fetal deaths/litter[c]	0.9 ± 0.6	2.0 ± 0.9	0.6 ± 0.4	1.6 ± 0.8
% Litters with one or more late fetal deaths	7	19	7	15
% Adversely affected implants/litter[c]	9.5 ± 1.8[§]	12.4 ± 2.3	6.9 ± 1.5	27.4 ± 4.9*
Live litters[d]				
Number of live fetuses/litter[c]	11.5 ± 0.6	10.9 ± 0.3	11.4 ± 0.4	10.0 ± 0.7
Average fetal body weight (g)/litter[c]				
Male fetuses[c]	1.08 ± 0.02[§]	1.03 ± 0.03	0.96 ± 0.02*	0.71 ± 0.02*
Female fetuses	1.04 ± 0.02[§]	0.99 ± 0.02	0.92 ± 0.02*	0.69 ± 0.01*
% Malformed fetuses/litter[c]	2.7 ± 1.2[§]	4.5 ± 1.9	1.6 ± 0.7	9.1 ± 2.4*
% Litters with one or more malformed fetuses				
All malformations	22	22	19	44
Gross malformations	7	4	4	16
Visceral malformations	4	7	6	4
Skeletal malformations	11	15	15	28
% Litters with variations	96	66*	70*	80
% Fetuses with variations/litter[c]	29.1 ± 3.5	18.8 ± 4.1*	11.9 ± 2.4*	26.3 ± 5.9

[a]NTP (1990a); Heindel et al. (1992).
[b]Includes all dams pregnant at sacrifice; litter size = number of implantation sites per dam.
[c]Mean ± standard error of the mean (SEM).
[d]Includes only dams with live fetuses; litter size = number of live fetuses per dam.

*$p < 0.05$, group comparisons versus controls
[§]$p < 0.05$, test for linear trend.

Table B.8. Histopathology in the Nasal Mucosa of Rats Exposed to HCl via Inhalation, 6 Hours/Day, 5 Days/Week, Until Natural Death—Up to 128 Weeks[a,b]

	Hydrogen Chloride 10 ppm (15 mg/m^3)[c]	Controls (Air Only)
Nasal mucosa		
No. animals examined	99	99
Epithelial or squamous hyperplasia	62	51
Squamous metaplasia	9	5

[a]Sellakumar et al. (1985); U.S. EPA (1995).
[b]Incidence of hyperplasia in the laryngeal-tracheal segment was increased to 24% in exposed animals vs. 6% in controls; however, individual animal data were not available, and incidence data did not distinguish between animals who had hyperplasia in both the larynx and the trachea and those with hyperplasia in either the larynx or the trachea (i.e., some animals were double-counted).
[c]Statistical significance not reported for any nonneoplastic effects in this study.

APPENDIX C. BMD OUTPUTS

Please see Appendix B of the IRIS Toxicological Profile for Boron and Compounds (U.S. EPA, 2004, pp. 125−130) for details of the BMD analysis.

APPENDIX D. REFERENCES

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