ACUTE TOXICITY

Acute Exposure Guideline Levels (AEGLs). 2005. Acute Exposure Guideline Levels (AEGLs) for 1,3-butadiene (CAS Reg. No. 106-99-0). Interim. Available from: www.epa.gov/oppt/aegl.

- Table 2. Narcosis and mortality in mice exposed to different 1,3-butadiene/O2 mixtures (killian 1930)
- Table 3. Summary of acute lethal inhalation data in laboratory animals
- Nonlethal toxicity via inhalation route [(AEGL 2005) Pages 8-9, excluding reproductive/developmental effects]

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

United States Environmental Protection Agency (USEPA). 2002. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F. National Center for Environmental Assessment, Office of Research and Development, Washington D.C.

- Table 5-1. A summary of the reproductive and developmental effects of 1,3-butadiene

ACUTE, INTERMEDIATE, CHRONIC TOXICITY

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

- Table 17. Toxicologic effects of Inhaled 1,3-butadiene

TABLE 2. Narcosis and mortality in mice exposed to different 1,3-butadiene/O_2 mixtures (Killian 1930)

Butadiene/O_2 (%)	Excitation	Spontaneous lateral position	Narcosis	Remarks
10/90	Imbalance after 5 min	Drowsy after 21 min	--	--
15/85	60 s	7 min	No true narcosis	Hyperventilation; marked spontaneous spasms
20/80	30-40 s	50-60 s	6-10 min	Extraordinary marked hyperventilation, labored respiration
25/75	Not marked	50-60 s	2-3 min	Hyperventilation; spontaneous spasms; deep sleep
30/70	20-30 s	40-50 s	1-1.2 min	Similar but stronger effects
40/60	Not marked	20-30 s	40-60 s	All dead in 11-14 min; respiratory paralysis

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals				
Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rabbit	150,000 250,000	25 min unknown	No mortality Mortality	Larionov *et al.* (1934)
Guinea pig	50,000 89,000 89,000 200,000 200,000	12 h 2 h 10 h 30 min 1 h	3/5 deaths 100% survival 100% mortality 100% survival 1/5 deaths	ERPG (1997)
Rat	50,000 89,000 89,000 200,000	24 h 6 h 18 h 30 min	100% survival 100% survival 5/7 deaths 2/5 deaths	ERPG (1997)
Rat	79,000 128,000 207,000	4 h	LC_{16} LC_{50} LC_{84}	Shugaev (1969)
Rat	2000-4000	15 h	0/2 deaths	Kreiling *et al.* (1987)
Mouse	10,000	2 h	100% survival	Bucher *et al.* (1993)
Mouse	91,000 122,000 169,000	2 h	LC_{16} LC_{50} LC_{84}	Shugaev (1969)

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals				
Mouse	2000-4000	15 h	lethality	Kreiling *et al.* (1987)

Nonlethal toxicity via inhalation route [1]			
Species	**Dose and time of exposure**	**Effects**	**Reference**
dogs (female)	0, 600, 2300 or 6700 ppm; 7.5 h/d for up to 8 months	Ophthalmoscopic examination of the eyes; no signs of injury	Carpenter et al. (1944)
rabbits	250,000 ppm, 1.6 min 250,000 ppm, 4.6 min 250,000 ppm, 7.4 min	Light anesthesia; Excitation and tremors Involuntarily blinking of the pupil	Carpenter et al. (1944)
rabbits	6700 ppm; 7.5 h/d for up to 8 months	Ophthalmoscopic examination of the eyes; no signs of injury	Carpenter et al. (1944)
rabbits	90,000 ppm; 2 hrs	Mild leucocytosis (3-10 days after exposure); neutrophilia, lymphopenia, and monocytosis were reported to occur. Bone marrow cell proliferation (10-20 days postexposure)	Pokrovski and Volchovka 1968
rabbits	150,000 ppm; 25 min	Irritation of conjunctiva and the nose, and lachrymation	Larionov et al. (1934)
rats (female)	7647 ppm; 6 h/d; GD 6-15	No respiratory distress	Irvine 1981
rats (Sprague Dawley)	201 ppm; 6 h	DNA-adduct study, no signs of toxicity	Boogaard et al. 2004)
rats (male and female)	0, 1000, 2000, 4000, or 8000 ppm for 6 h/d, 5 d/w for 3 months	No effects attributed to exposure were found (no effects on cholinesterase activity in brain or erythrocytes; no effects on neuromuscular function tests	Crouch et al. 1979)
mice (male and female)	0, 1000, 5000, or 10,000 ppm for two hrs, then followed for lifetime	incidence of neoplastic and nonneoplastic lesions were not affected	Bucher et al. (1993)
mice	90,000 to 140,000 ppm	The first signs of toxicity included irritation of the conjunctiva and nose. Death occurred	Larionov et al. (1934)
mice	0, 199, 999, or 4980 ppm; 6 h/d for 5 successive days	No clinical sign of toxicity were observed apart from piloerection and dyspnea during the first 20-30 min of the exposure in the 4980 ppm exposure group	Hackett et al. (1988, summarized by Morrisey et al. 1990, EPA 2002)
mice (male)	0, 130, 500, or 1300 ppm; inhalation; 6 h/d for 5 successive days	statistically significantly decreased testis weight in the 1300 ppm exposure group at two weeks after the mating period	Pacchierotti et al (1998)
mice (male)	20l ppm for 6 hrs followed by a 42-hr observation period	DNA-adduct study, no signs of toxicity	Boogaard et al. 2004)

1 Acute Exposure Guideline Levels (AEGLs). 2005. Acute Exposure Guideline Levels (AEGLs) for 1,3-butadiene (CAS Reg. No. 106-99-0). Interim. Available from: www.epa.gov/oppt/aegl. [Pages 8-9, excluding reproductive/developmental effects]

Table 5-1. A summary of the reproductive and developmental effects of 1,3-butadiene.

Species	Dose, route, and time of exposure	Effects	LOAEL[a]	Reference
Reproductive Effects				
Male and female rats, guinea pigs, rabbits; female dogs	0, 600, 2,300, 6,700 ppm, 7.5 hr/day, 6 days/wk, 8 mos	↓ body wt in rats, guinea pigs; mild cloudy swelling in liver at 6,700 ppm in all species; ↓ fertility in rats	no statistical analysis	Carpenter et al., 1944
Male and female rats	0, 1,000, 8,000 ppm, 6h/day, 5 days/wk, 105 wks (females), 111 wks (males)	↑ mortality with exposure; benign and malignant mammary tumors, uterine sarcomas, thyroid follicular cell tumors (females); Leydig cell tumors, pancreatic exocrine adenomas (males)	1,000 ppm for 105 or 111 wks >8,000 ppm for non-neoplastic lesions	Owen et al., 1987; Owen and Glaister, 1990
Male and female $B6C3F_1$ mice	0, 625, 1,250 ppm, 6 hr/day, 5 days/wk, 60 or 61 wks	↑ mortality; numerous neoplasms including mammary gland; ovarian atrophy, uterine atrophy, (females); testicular atrophy (males)	625 ppm for 60 or 61 wks	NTP, 1984
Male and female $B6C3F_1$ mice	0, 6.25, 20, 62.5, 200, 625 ppm, 6 hr/day, 5 days/wk, 103 wks (some killed at 9 and 15 mos)	↑ mortality (≥ 20 ppm); ovarian atrophy, germinal epithelial hyperplasia, angiectasis, granulosa cell tumors, uterine atrophy, mammary tumors (females); testicular atrophy (males)	6.25 ppm for 103 wks 62.5 ppm for 15 mos 200 ppm for 9 mos	NTP, 1993
Male and female rats and mice	0, 1,000 ppm, 6 hr/day, 5 days/wk, 13 wks	no effects on reproductive system (rats); ovarian atrophy (female mice); testicular atrophy (male mice)	1,000 ppm[b] for 13 wks in mice	Bevan et al., 1996

United States Environmental Protection Agency (USEPA). 2002. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F. National Center for Environmental Assessment, Office of Research and Development, Washington D.C.

Table 5-1. A summary of the reproductive and developmental effects of 1,3-butadiene (continued).

Species	Dose, route, and time of exposure	Effects	LOAEL[a]	Reference
Reproductive Effects (continued)				
Male B6C3F$_1$ mice (sperm head morphology study)	0, 200, 1,000, 5,000 ppm, 6 hr/day, 5 days; killed at 5 wks after exposure	↓ % epididymal sperm, ↑ sperm head abnormalities	1,000 ppm for 5 days	Hackett et al., 1988a
Male 102/E1XC3H/E1 mice (flow cytometric analysis of spermatogonial cells)	0, 130, 500, 1,300 ppm, 6 hr/day, 5 days; killed 21 days after exposure and later	↓ testis weight, ↓ round and elongated spermatids	130 ppm for 5 days	Pacchierotti et al., 1998b
Developmental Effects				
Pregnant CD rats	0, 200, 1,000, 8,000 ppm, 6 hr/day, GD 6-15; killed GD 20	↑maternal toxicity, ↓ fetal body wt and CRL, ↑ skeletal and eye defects	1,000 ppm for 10 days	IISRP, 1982
Pregnant CD rats	0, 40, 200, 1,000 ppm, 6 hr/day, GD 6-15	↑maternal toxicity, no fetal effects	1,000 ppm for 10 days	Hackett et al., 1987a
Pregnant CD-1 mice	0, 40, 200, 1,000 ppm, 6 hr/day, GD 6-15	↑ maternal toxicity, ↓ fetal wt, ↑ skeletal variants	40 ppm for 10 days	Hackett et al., 1987b

[a] Lowest-observed-adverse-effect-level

[b] Frank effects on ovarian and testicular atrophy at this exposure level, not a LOAEL.

United States Environmental Protection Agency (USEPA). 2002. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F. National Center for Environmental Assessment, Office of Research and Development, Washington D.C.

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

TABLE 17. Toxicologic Effects of Inhaled 1,3-Butadiene [a]

Toxicity Classification	Species (Gender)	Exposure frequency and duration	Butadiene exposure concentration (ppm)	Effect	Reference
Acute Exposure (≤14 days):					
Lethality	Mouse (strain not stated)	1 d 2 h	122,000	Lethal concentration, 50% killed	Shugaev (1969)
	Rat (strain not stated)	1 d 4 h	129,000	Lethal concentration, 50% killed	
	Rabbit (male and female, strain not stated)	1 d 23 min	250,000	Death following anesthesia.	Carpenter et al. (1944)
Neurological	Human (male)	1 d 6-8 h	8000	No effect.	Carpenter et al. (1944)
	Rabbit (male and female, strain not stated)	1 d 23 min	250,000	Anesthesia.	Carpenter et al. (1944)
Developmental	Sprague-Dawley rat (female)	10 d 6 h • d^{-1} GD 6-15	200 1000 8000	Reduced maternal weight gain. Wavy ribs. Skeletal abnormalities.	Irvine (1981)
	CD-1 Swiss mouse (female)	10 d 6 h • d^{-1} GD 6-15	40 200	Decreased fetal weight. Extra ribs.	Morrissey et al. (1990)
	Sprague-Dawley rat (female)	10 d 6 h • d^{-1} GD 6-15	40 and 200 1000	No effect. Reduced maternal body weight gain, no fetal toxicity	Morrissey et al. (1990)
Reproductive	B6C3F1 mouse (male)	5 d 6 h • d^{-1}	1000	Sperm head abnormalities.	Morrissey et al. (1990)
	CD-1 Swiss mouse (male)	5 d 6 h • d^{-1}	200	Dominant lethal study; males exposed to butadiene and mated to nonexposed females resulted in dead implantations.	Morrissey et al. (1990)
	(102/E1 x C3H/E1) F1 mouse (male)	5 d 6 h • d^{-1}	1300	Dominant lethal study; males exposed to butadiene and mated to nonexposed females resulted in dead implantations.	Adler et al. (1994)
Biochemical	B6C3F1 mouse (male)	5 d 6 h • d^{-1}	0 740	Control. No induction of butadiene metabolism was observed in liver microsomes prepared from B6C3F1 mice; butadiene exposure depressed microsomal lung metabolism by 50%.	Bond et al. (1988)
	Sprague-Dawley rat (male)	5 d	0	Control.	

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

TABLE 17. Toxicologic Effects of Inhaled 1,3-Butadiene [a]

Toxicity Cassification	Species (Gender)	Exposure frequency and duration	Butadiene exposure concentration (ppm)	Effect	Reference
		6 h • d^{-1}	7600	No induction of butadiene metabolism was observed in liver microsomes prepared from Sprague-Dawlry rats; butadiene exposure depressed microsomal lung metabolism by 50%.	
	B6C3F1 mouse (male)	1 d 7-15 h	2000- 3000	Liver GSH was 80% of control after 7 h and 96% of control after 15 h of exposure	Kreiling et al. (1988)
	Sprague-Dawley and Wistar rat (male)	1 d 7-15 h	2000- 3000	Liver GSH was 20% and 35% of control in Sprague-Dawley and Wistar rats respectively after 7 or 15 h of exposure.	
	B6C3F1 mouse (male)	1 d 7 h	0-2000 <100 250 500 1000 2000	Measured dose response for GSH depletion in lung > liver > heart after 7 h exposure. Not different from control. All tissues 10-20% depletion of GSH. Lung, 50% depletion; liver, 40% depletion; heart, 20% depletion. Lung, 80-90% depletion; liver, 60% depletion; heart, 20% depletion. Lung, 95% depletion; liver, 80% depletion; heart, 70% depletion.	Deutschmann and Laib (1989)
	Sprague-Dawley rat (male)	1 d 7 h	0-2000 <100 250-1000 1000 2000	Measured dose response for GSH depletion in liver > lung > heart after 7 h exposure. Not different from control. Liver, 20% depletion. Lung, 20% depletion. Liver, 60% depletion; lung, 20% depletion; heart, no change.	
	Wistar rat (male)	5 d 6 h • d^{-1}	0 500	Control. Induction of the cytochrome P450 CYP 2E1 isozyme, as measured by monoclonal antibody-Western blot; the magnitude of induction ranged from 1.2 to 1.5 times greater in liver microsomes of butadiene-exposed rats compared to controls for styrene epoxidation, ECOD, NDMAD, and epoxide hydrolase.	Elovaara et al. (1994)
	B6C3F1 mouse (male)	1 d 6 h	625 1250	Lung, 30% GSH depletion after 3 h exposure. Liver, 45% GSH depletion after 6 h exposure.	Himmelstein et al. (1995)
	Sprague-Dawley rat (male)	1 d 6 h	1250	Lung, 25% GSH depletion after 6 h exposure. Liver, 40% GSH depletion after 6 h exposure.	
Intermediate Exposure (15–364 days):					
Death	Sprague-Dawley rat (male and female)	13 wk	8000	No effect.	Crouch et al. (1979)

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

TABLE 17. Toxicologic Effects of Inhaled 1,3-Butadiene [a]

Toxicity Cassification	Species (Gender)	Exposure frequency and duration	Butadiene exposure concentration (ppm)	Effect	Reference
		5 d • wk^{-1} 6 h • d^{-1}			
	B6C3F1 mouse (male and female)	14 wk 5 d • wk^{-1} 6 h • d^{-1}	2500 5000	No effect. Increased mortality.	NTP (1984)
Systemic	Sprague-Dawley rat (male and female)	13 wk 5 d • wk^{-1} 6 h • d^{-1}	8000	No effects noted for respiratory tract, cardiovascular, hematological, liver, kidney, skin or eye.	Crouch et al. (1979)
	B6C3F1 Mouse (male and female)	14 wk 6 h • d^{-1}	8000	No effects noted for respiratory tract, cardiovascular, skin or eye.	NTP (1984)
	B6C3F1 and NIH Swiss mouse (male)	3-24 wk 6 d • wk^{-1} 6 h • d^{-1}	1250	Hematological, macrocytic megaloblastic anemia.	Irons et al. (1986a,b)
Immunologic	B6C3F1 mouse (male)	6-24 wk 5 d • wk^{-1} 6 h • d^{-1}	1250	Increased extramedullary hematopoiesis and reduced lymphoid cellularity of the spleen.	Thurmond et al. (1986)
Neurological	Sprague-Dawley rat (male and female)	13 wk 5 d • wk^{-1} 6 h • d^{-1}	8000	No effect.	Crouch et al. (1979)
	B6C3F1 mouse (male and female)	14 wk 5 d • wk^{-1} 6 h • d^{-1}	8000	No effect.	NTP (1984)
Reproductive	CD-1 mouse (male)	10 wk 5 d • wk^{-1} 6 h • d^{-1}	1250	Dominant lethal study; males exposed to butadiene and mated to nonexposed females resulted in dead implants.	Anderson et al. (1993)
Cancer	B6C3F1 mouse (male and female)	13-52 wk 5 d • wk^{-1} 6 h • d^{-1}	200	Cancer; see Table 19 of this review.	NTP (1993); Melnick et al. (1990b)

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

TABLE 17. Toxicologic Effects of Inhaled 1,3-Butadiene [a]

Toxicity Cassification	Species (Gender)	Exposure frequency and duration	Butadiene exposure concentration (ppm)	Effect	Reference
Chronic Exposure (≥365 days):					
Death	Sprague-Dawley rat (male and female)	105-111 wk 5 d • wk^{-1} 6 h • d^{-1}	1000 8000	No effect. Increased mortality due to cancer; see Table 18.	Owen et al. (1987)
	B6C3F1 mouse (male and female)	61 wk 5 d • wk^{-1} 6 h • d^{-1}	625	Increased mortality due to cancer; see Table 19.	NTP (1993); Huff et al. (1985)
	B6C3F1 mouse (male and female)	65 wk 5 d • wk^{-1} 6 h • d^{-1}	6.25 20	No effect. Increased mortality due to cancer, see Table 19.	NTP (1993); Melnick et al. (1990b)
Systemic	Sprague-Dawley rat (male and female)	105-111 wk 5 d • wk^{-1} 6 h • d^{-1}	1000 8000 1000 8000	No effect in respiratory tract. Increased organ weight, metaplasia. No effect in kidney. No effect for cardiovascular, gastrointestinal, hematological, liver, skin, eye.	Owen et al. (1987)
	B6C3F1 mouse (male and female)	61 wk 5 d • wk^{-1} 6 h • d^{-1}	625 1250	Cardiovascular, endothelial hyperplasia; gastrointestional, epithelial hyperplasia; hepatic necrosis. Respiratory tract, atrophy of nasal olfactory epithelium. No effect for kidney, skin, eye.	NTP (1993)
	B6C3F1 mouse (male and female)	65 wk 5 d • wk^{-1} 6 h • d^{-1}	20 62.5	No effects noted in respiratory tract, cardiovascular, gastrointestional, hematological. Respiratory tract, cardiovascular, gastrointestional, hematological; epithelial hyperplasia.	
Neurological	Sprague-Dawley rat (male and female)	105-111 wk 5 d • wk^{-1} 6 h • d^{-1}	8000	No neurological effect.	Owen et al. (1987)
	B6C3F1 mouse (male and female)	61 wk 5 d • wk^{-1} 6 h • d^{-1}	1250	No neurological effect.	NTP (1984)
Reproductive	B6C3F1 mouse (male)	61 wk 5 d • wk^{-1} 6 h • d^{-1}	625	Testicular atrophy.	NTP (1993)

Himmelstein, MW, JF Acquavella, L Recio, et al. 1997.Toxicology and epidemiology of 1,3-butadiene, *Crit Rev Toxicol* 27: 1-108.

TABLE 17. Toxicologic Effects of Inhaled 1,3-Butadiene [a]

Toxicity Cassification	Species (Gender)	Exposure frequency and duration	Butadiene exposure concentration (ppm)	Effect	Reference
	B6C3F1 mouse (female)	65 wk 5 d • wk^{-1} 6 h • d^{-1}	6.25	Ovarian atrophy was dose-dependent and occurred earlier in animals exposed to higher concentrations of butadiene.	NTP (1993); Melnick et al. (1990b)
Cancer	Sprague-Dawley rat (male and female)	105-111 wk 5 d • wk^{-1} 6 h • d^{-1}	1000	Cancer; see Table 18	Owen et al. (1987)
	B6C3F1 mouse (male and female)	61 wk 5 d • wk^{-1} 6 h • d^{-1}	625	Cancer; see Table 19.	NTP (1984)
	B6C3F1 mouse (female)	65-104 wk 5 d • wk^{-1} 6 h • d^{-1}	6.25	Cancer; see Table 19.	NTP (1993); Melnick et al. (1990b)

Abbreviations: d = day; ECOD = 7-ethoxycoumarin O-deethylation; GD = gestation day; GSH = glutathione, measured as nonprotein sulfhydryl content; NDMAD = N-nitrosodimethylamine N-demethylation; ppm = parts per million.

[a] Modified from the Agency for Toxic Substances and Disease Registry (ATSDR), 1992.