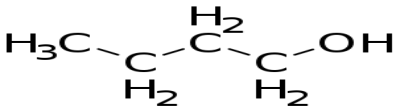
Substance name: n-butanol

CAS: 71-36-3 **MW**: 74.12 gm/mole

- Synonyms: Butanol; n-butyl alcohol; butyl alcohol; butyl hydroxide

Molecular formula: $C4H_{10}O$ Structural formula: 

Conversion factor: (at NTP): 1 ppm = 3.03 mg/m^3

Physical characteristics at room temp:

boiling point 243.9 ^oF
melting point -129.6 ^oF
vapor pressure 6 mmHg
solubility 73 gm/l
density 0.81 gm/cm^3
Log P_{ow} 0.839

Special physical characteristics if any:

Colorless refractive liquid with a banana-like, harsh, alcoholic and sweet odor.

Flammability and other hazards:

Flash point 77 ^oF (closed cup)

Uses/applications: Butyl alcohol is used predominately as an industrial intermediate. For example, it is used to make butyl acetate and other butyl esters; butyl ethers, such as ethylene glycol monobutyl ether, di- and triethylene glycol monobutyl ether, and the corresponding butyl ether acetates. It is used to manufacture dibutyl phthalate, pharmaceuticals, polymers, pyroxylin plastics, butyl xanthate and other butyl compounds. Butyl alcohol is used as a diluent/reactant in the manufacture of urea/formaldehyde and melamine/formaldehyde resins. When used as an industrial intermediate, butyl alcohol is consumed by chemical conversion to the desired product. Butyl alcohol is used to a lesser extent as a solvent and in formulations to make, dyes, lacquers (including cellulose lacquers), resins and varnishes. It is a component in some nail polish formulations. It is used to make rubber cement, safety glass, rayon, waterproofed cloth, artificial leather, raincoats, motion picture and photographic film. It is used as a softener in the fabrication of cellulose nitrate plastics (Tabershaw et. al., 1944; Cogan and Grant, 1945; Sterner et al., 1949; Mellan, 1950; Doolittle, 1954). It is also used in the manufacture of pharmaceuticals, in microscopy (preparing paraffin imbedding materials), in veterinary medicine (as a bactericide), as a dehydrating agent, in perfumes, fruit essences, and as a flavoring agent in foods and beverages (Genium, 1993; Hall and Oser, 1965).

Organizational sources and recommendations (freehand or table format)

TLV, WEEL, REL, OEHHA RELs and Prop 65, NTP, EPA, IARC, EU, OECD, Hazard Profiles Canada

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
Cal/OSHA Title 8	PEL 50 ppm; STEL - NA		
Fed-OSHA	PEL 100 ppm TWA		
NIOSH IDLH	1400 ppm	safety considerations, NIOSH IDLH Table	10% if the lower explosive limit of 1.4%
NIOSH REL	Ceiling 50 ppm; skin	NIOSH, 1992	
ACGIH TLV (2005)	TWA 20 ppm;	irritation	
MAK (current)	TWA 100 ppm	irritation	

Other recommendations

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Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA – REL	No determination		
OEHHA – Prop 65	No determination	-	-
US EPA	No determination	-	-
NTP - RoC	No evidence	-	-
ATSDR	No determination	-	-
IARC	No determination	-	

Studies Reviewed

Animal Studies

There are no chronic animal studies of n-butanol exposure through any exposure route (USEPA, 2011). A limited number of subchronic inhalation studies are available for n-butanol; these studies have predominantly examined developmental and neurological effects while a few studies have included hematological and reproductive effects. Studies considered acceptable for hazard assessment are included in Table 1.

Korsak et al. (1994) exposed male Wistar rats (12/exposure group, 24 controls) to n-butanol vapor concentrations of 0, 50, or 100 ppm (0, 154, or 308 mg/m3) 6 hours/day, 5 days/week, for 3 months. Rotorod performance (balance on rotating bar) was evaluated during and hot-plate behavior (latency of pain sensitivity) immediately at the end of exposure. Hematological parameters and clinical biochemistry were analyzed. There were dose- and duration-related increases in the percentage of rotorod test failures while there were no effects on pain sensitivity. The investigators reported that

increased failure rates in the 100 ppm group were statistically significant during the second and third months of exposure; the changes in the low exposure group were not statistically significant at any time point. The failure rates in both exposed groups increased linearly with duration of exposure. This increase over time indicates that there was no adaptation to treatment occurring within the study period and suggests that adaption would not occur if there was continued exposure. Compared to controls, the exposed groups exhibited decreased erythrocyte counts (5 and 16% lower in the 154 and 308 mg/m3 groups, respectively); the difference was statistically significant in the 308 mg/m3 group. Statistically significantly decreased hemoglobin levels (10% lower than controls) were noted in both exposure groups, but hematocrit was not changed. There were increased leukocyte counts (25 and 57% higher in the 154 and 308 mg/m3 group, respectively); the difference was statistically significant in the 308 mg/m3 group, and was beyond the normal range of variability (16.5 × 103/nm3 in exposed rats, compared with a range of 1.96–8.25 × 103/nm3. EPA identified NOAEL and LOAEL values of 50 ppm and 100 ppm, respectively, based on increases in the percentage of rotorod test failures in rats. Decreased hemoglobin and increased lipid peroxidation were both observed at the NOAEL; however, EPA judged the changes at that concentration not to be biologically significant (EPA, draft, YEAR)

Nelson et al. (1989a) exposed Sprague-Dawley rats in a chamber to n-butanol vapor at nominal concentrations of 0, 3,500, 6,000, or 8,000 ppm, 7 hours/day on gestational days 1–19. Exposure to n-butanol had no effect on number of corpora lutea, resorptions or live fetuses/litter, or sex ratio. External malformations were not observed in any group. Statistically significant concentration-related reductions in body weight were observed in male and female fetuses at the mid- and high-exposure levels (12 and 24–27% lower than controls in the 18,000 and 24,000 mg/m3 groups, respectively). The percent of fetuses having normal skeletal development was statistically significantly lower at 24,000 mg/m3 n-butanol. Based on the increased incidence of litters with skeletal variations EPA identified the LOAEL as 3,500 ppm; a NOAEL was not identified. (REF)

Nelson et al. (1989b) evaluated behavioral teratology in young rats following in utero or paternal inhalation exposure to n-butanol vapor. Groups of 15 pregnant female Sprague-Dawley rats were exposed to 0, 3,000, or 6,000 ppm n-butanol for 7 hours/day on gestational days 1–19 (termed “maternal exposure group” by the authors). Groups of 18 male Sprague-Dawley rats were exposed to the same concentrations of n-butanol for 7 hours/day for 6 weeks and then mated to non-butanol exposed females (termed “paternal exposure group” by the authors). There were no behavioral changes in the offspring in terms of their performance in ascent test, rotorod performance, open field performance, or operant conditioning. In offspring of 18,000 mg/m3 paternal exposure group, the time receiving shock and the total number of times that rats crossed from one side of the cage to the other were both statistically significantly increased over controls. Monitoring of photoelectric activity showed statistically significantly lower counts in female offspring of to the 9,000 mg/m3 paternal exposure group but not in offspring of the high-concentration paternal exposure group (data not shown and magnitude of change not reported).

Table 1

Study/Type	Effect Measures		Results	NOAEL
Korsak, 1994 Subchronic inhalation	Neuromuscular /neurological effects assessed with rotorod performance (balance on rotating rod) and hot-plate	Wistar rat 12 male/exposre; 24 controls 0, 50, or 100 ppm 6 hr/d, 5 d/wk for 3 months.	There were no significant differences in mean body weights or absolute or relative organ weights after 3 months. Hemoglobin and erythrocytes significantly lower and leukocytes and eosinophils significantly higher in the 100 ppm group; only hemoglobin was significantly lower in the 50 ppm group. Increased failure	50 ppm

	behavior (latency of response). Terminal body weight and organ weights recorded. Hematological parameters/clinical biochemistry analyzed.		rates in the 308 mg/m3 group were statistically significant during the second and third months of exposure; the changes in the low exposure group were not statistically significant at any time point. The failure rates in both exposed groups increased linearly with increasing duration of exposure. Lipid peroxidation increased significantly in both groups.	
Nelson, 1989a Developmental	Numbers of corpora lutea, resorptions and live fetuses were recorded. Fetuses were weighed, sexed, and examined for external malformationsHalf of the fetuses examined for skeletal malformations and the other half for visceral malformations	Sprague-Dawley rats (15-20 per group) exposed to n-butanol vapor at 0, 3,500, 6,000, or 8,000 ppm, 7 hours/day on GDs 1–19. .	No effect on number of corpora lutea, resorptions or live fetuses/litter, or sex ratio. External malformations were not observed in any group. Significant concentration-related reductions in body weight were observed in male and female fetuses at the mid- and high-exposure levels (12 and 24–27% lower than controls in the 6,000 and 8,000 ppm groups, respectively). The percent of fetuses having normal skeletal development was statistically significantly lower at 8,000 ppm n-butanol. Based on Fisher's exact tests performed by EPA, the incidence of litters with skeletal malformations was significantly increased at all concentrations and the incidence of litters with visceral malformations was significantly increased at the highest concentration. EPA identified the lowest concentration tested (11,000 mg/m3 or 3,500 ppm) as a LOAEL based on the increased incidence of litters with skeletal variations; a NOAEL was not identified.	3,500 LOAEL
Nelson, 1989b Developmental/ neurobehavioral	F0 exposed prior to mating and during gestation; F1 subjected to behavioral testing of neuromotor coordination, activity and learning. Fourth group used for brain neurotransmitter analysis.	Sprague-Dawley rat; 15 pregnant females and 18 males/group exposed to 0, 9,000, 318,000 mg/m 7 hr/d on GDs 1–19 (females) or for 6 wks prior to mating with nonexposed females (males)	No behavioral changes in the offspring in performance in ascent test, rotorod performance, open field performance, or operant conditioning. Neurotransmitter concentrations were significant increased in the overall concentration of serotonin (mean ± SEs were 14.48 ± 2.38 versus 7.802 ± 1.48 in controls; units not reported) and dopamine (0.715 ± 0.127 versus 0.515 ± 0.095 in controls; units not reported) in offspring of the 18,000 mg/m3 paternal exposure group. No other significant changes in neurotransmitter concentrations associated with exposure to n-butanol. EPA identified the highest concentration tested as a NOAEL based on a lack of neurobehavioral effects in offspring. (EPA, YEAR, draft).	6,000 ppm
David, 1998 Subchronic	Subchronic neurotoxicity of n-butyl acetate	Sprague-Dawley rats exposed to 0,	Transient signs of sedation and hypoactivity were observed only during exposure to the 1500 and 3000 ppm concentration. No evidence of	1,500 ppm

neurotoxicity n-butyl acetate	investigated by functional observational battery (FOB), motor activity, neurohistopathology and schedule-controlled operant behavior (SCOB) as indicators of neurotoxicity	500, 1500, or 3000 ppm of n-butyl acetate for 6 hr/5 days over 14 weeks. FOB and motor activity measured during Weeks 1, 4, 8, and 13. SCOB testing was conducted daily. Weeks - 1, 4, 8, and 13 were evaluated for evidence of neurotoxicity.	neurotoxicity in FOB examinations. Motor activity for the 3000 ppm male group was significantly (p < or = 0.05) higher than for the control group only during Week 4. No significant differences in motor activity values were observed for female rats. No significant differences were seen in SCOB at any test vapor concentration. Microscopic evaluations of sections from the brain, spinal cord, dorsal and ventral spinal roots, dorsal root ganglia, sciatic nerve, and tibial nerve of animals in the control and 3000 ppm groups did not indicate any treatment-related effects.	
David 2001 Subchronic toxicity n-butyl acetate	Organ weights recorded for all groups; blood samples analyzed hematological parameters, serum samples for enzyme, electrolyte and protein levels. The number of elongated spermatids (testes) or spermatozoa (epididymis) were counted.	Male and female Sprague–Dawley (SD) rats exposed to 0, 500, 1500 or 3000 ppm nBA for 6 h per day, 5 days per week for 13 weeks	3000 ppm group had reduced activity levels of generally minor severity during exposure. Body weight significanlty lower in 1500 (73.5% of controls) and 3000 ppm groups (70% of controls) (P<0.05). Significantly higher mean erythrocyte counts, hemoglobin concentration and hematocrit values were observed for the 3000 ppm male and female rats but these fell within normal range and were not considered biologically significant. No dose-related or statistically significant effect on epidydimidal or testicular sperm count was observed compared with controls, although the epididymidal sperm counts for all treated groups were lower than controls. Degeneration of the olfactory epithelium along the dorsal medial meatus and ethmoturbinates of the nasal passages of some 1500 and all 3000 ppm rats was seen. The severity was mild to moderate for the 3000 ppm group and minimal to mild for the 1500 ppm group.	500 ppm Body weight and olfactory lesions

Humans Studies

Occupational studies of n-butanol are constrained by the presence of co-exposure to multiple solvents (toluene and xylene most commonly) though there are several studies of exposure to only n-butanol (Tabershaw, Velazquez and Sterner). Most of these studies were conducted in the 1940's as workplace investigations. The studies consisted of workplace investigations of reports/cases of eye irritation with subsequent control measures reducing the level of those incidents. All exposure data in these studies were obtained by area sampling. Eye irritation was the most prevalent effect

observed in these studies. The Velasquez study (1969) was found to be inadequate for health assessment due to methodological issues and small sample size (IRIS, ####; ACGIH, 2002).

Table 2: Occupational studies of n-butanol exposure

Study	N	Effects Studies	Concentration	Results
Tabershaw et al., 1944	Not reported	Eye irritation, dermatitis, and systemic effects were evaluated in workers from six facilities. n-butanol was sole solvent used in two facilities and was used in combination with MEK, ethyl alcohol, diacetone alcohol and naptha in other plants.	Butanol-only facilities: 5–14 ppm 20–65 ppm (61–197 mg/m	Eye irritation reported at concentrations ranging from 20 to 115 ppm in 5 of the 6 facilities, eye irritation was reported. In butanol-only facilities, no symptoms were reported at 5 – 14 ppm whereas workers in the other butanol-only facility reported eye irritation between 20 – 65 ppm. Frequency of complaints in decreasing order were: 1) irritation of the eyes leading to a particular type of corneal inflammation, 2) disagreeable odor, 3) slight headache and vertigo, 4) slight irritation of the nose and throat, and 5) dermatitis of the fingers and hands.
Velazquez et al., 1969	11 butanol + noise (72–78 db), 47 noise only (90–110 db)	Audiologic effects of n-butanol-exposed workers were compared with workers from another factory exposed to higher noise levels but not n-butanol or other solvents associated with hearing loss.	80 ppm as measured by gas chromatography (GC) in work room at a cellulose acetate ribbon factory	Hearing loss was observed in 9/11 workers exposed to n-butanol and in 23/47 workers without exposure to n-butanol but with exposure to industrial noise. The effect levels and sampling protocol for measurement of n-butanol was not described.
Cogan et 1945 et al.	75 female workers	Eye examinations were performed on symptomatic workers employed at a facility reported in the Tabershaw study.	15–100 ppm, ethanol and diacetone alcohol (concentrations unknown)	Twenty-eight of 35 workers exposed to n-butanol exhibited evidence of corneal inflammation and no unexposed workers showed signs of inflammation. Exposure to multiple solvents. No effect levels were reported.
Sterner et al., 1949	16 male workers	Physical examinations (7) of workers exposed to n-butanol (n = 16) during coating of photographic paper	Initial concentrations of n-butanol averaged 200 ppm (606 mg/m3), but	Workers exposed to n-butanol concentrations averaging ≥200 ppm (606 mg/m3experienced corneal edema and mild edema of the conjuctiva. No irritation or other

		over 10-year paper were conducted. Measurements at breathing zone area.	decreased to 100 ppm (303 mg/m3) over the course of the study	symptoms were reported at 100 ppm. Only four subjects in the study remained at 10 yrs.

Several human exposure studies of n-butanol have been conducted. Irritation was the endpoint of interest in most of these studies. There are limitations in how to interpret these studies. In Nelson (1943), approximately 10 individuals were exposed inside a chamber for 3-5 minutes to 16 separate substances but the actual number exposed to n-butanol cannot be determined. The authors claim the short exposure was needed to accommodate volunteers but do not explain how the exposure protocol was conducted, specifically the rest time between the exposures. The studies by Kjaegaard and Hempel-Jùrgensen were by the same group and designed to evaluate the relationship between subjective and objective measures of irritation. The studies did not link the objective endpoints used (eye redness and cytological measures) to any clinical assessment of irritation.

Study	Exposure	Study Design	Results	Conclusion
Nelson, 1943	25, 50 ppm	Average of 10 people exposed in a 1200 ft^3 chamber for 3-5 minutes. After exposure, each individual classified the effect of the vapor on the eyes, nose, and throat. The classifications were: no reaction, slightly irritating, and very irritating. The odor was listed as absent, definite, moderate, strong, or overpowering.	The concentration that irritated eyes, noses and throats of a majority of individuals were 50, 25 and 25 ppm, respectively. There was a unanimous feeling of pronounced throat irritation, and several subjects complained of mild headache. A majority also concluded that the concentration satisfactory for 8-hr exposure was below 25 ppm.	Chamber concentrations estimated, not measured. LOAEL: 25 ppm
Kjaegaard. 1997	12 human subjects Chamber study of exposure n-butanol	Irritation assessed using a computerized questionnaire based on visual analogue scales (VAS) to quantify intensity. Intensity was indicated by positioning the cursor along a 0-25' point scale. General, eye, nose, and throat irritation and odor intensity were assessed. Subjects also reported continuously about eye, nose and throat irritation on a VAS scale by setting a linear potentiometer, every 3	12 subjects exposed to 0, 0.75, 1.5 and 3 ppm n-butanol (approximately) for 90 min. Responses used in these analyses were averages for all subjects.	Significant association between concentration and nose irritation ($p < 0.05$), general and eye irritation ($p< 0.01$) and throat irritation ($p< 0.001$). Average sensory eye, nose, and throat irritation plateaued to 15% when the subjects were exposed to 1.5 ppm and 27% when the subjects were exposed to 3 ppm. It cannot be determined from the

		minutes.		study whether reported responses rise to a level of clinical effect.
Hempel-Jùrgensen, 1998	8	Eye-exposure system used in conjuction with objective eye irritation measures (photographs of conjunctival hyperemia; conjunctival fluid cytology) in 8 humans. Pre- and post-exposure photographs were compared for hyperemia. Fluid stained and counted for PMNs, lymphocytes, cuboid epithelial cells, and squamous epithelial cells immediately after exposure.	One eye of subject exposed in two separate tests to 0, 99, 314, 990 ppm n-butanol for 60 minutes.	On a scale of 0-2, 0 being no post-exposure redness and 2 being most red after exposure, 0, 99, 314 and 990 ppm resulted in scores of 0.48 ± 0.96, 0.81 ± 1.09, 0.63 ± 1.15, and 1.40 ± 0.76. Only the 990 ppm treatment was significantly different from controls. No cytological changes were observed. NOAEL: 314 ppm

Mode of Action Studies

The irritative effects of the butyl alcohol isomers are likely the result of non-covalent interaction with the receptors of the sensory nerve endings in the mucous membranes of the respiratory tract and are a function of the physico-chemical properties (e.g. vapor pressure, lipophilicity) of the substances. The acute central nervous effects such as narcosis which occur at higher concentrations are probably the result of the interaction of the relatively hydrophobic substances with neuronal membranes, disrupting normal functioning (n-butyl alcohol, MAK documentation). For sub-chronic and chronic exposures specific neurotoxic effects observed with n-butanol likely involves interactions of biotransformation products with specific targets in the nervous system (ECHA reference). In animal studies with ethanol, some of these targets have been associated with both neuromuscular/activity effects and neurotoxic developmental effects.

Mechanistic data and some in vivo animal findings indicate that there are similar developmental neurotoxicity concerns from exposure to butanols. Multiple mechanisms for n-butanol developmental neurotoxicity have been proposed (reviewed in Bale, 2016) and the data summarized in EPA (YEAR). The data were obtained mostly in neuronal cell/membrane culture studies. A recent review of the butanol isomers concluded that the data somewhat suggest that there may be developmental neurotoxicity associated with the different butanol isomers but that more research is needed to conclusively determine if there is an actual association between butanol exposure and developmental neurotoxicity (Bale, 2016).

Some neurodevelopmental changes have been reported with n-butanol. In the five studies that evaluated developmental neurotoxicity endpoints from different routes, three studies (Sitarek et al., 1994; Nelson et al., 1989b; McLaughlin et al., 1964) reported significant changes with n-butanol exposure, and two studies (Ema et al., 2005; Nelson et al., 1989a) did not find any significant neurodevelopmental changes. Nelson (1989a; 1989b) represents the only animal studies demonstrating neurotoxic effects from n-butanol inhalation. Study details and results are summarized in Table X.

Table X. Neurotoxicity of n-butyl alcohol

Study	Exposure	Results	NOAEL/LOAEL
McLaughlin 1964 Bolus injection	Species: Chicken, n: >200 0, 8, 16, 24, 32 mg/egg	Increased incidence of corneal opacity (cataracts) and nerve damage at 320 and 480 mg/kg. No hatched eggs at 640 mg/kg.	
Sitarek 1994 Drinking water	Species: Rat Administered doses: 0 (n = 16), 300 (n = 17), 1000 (n = 17), 5000 (n = 11) mg/kg/day for 8 0 (n = 16), 300 (n = 17), 1000 (n = 17), 5000 (n = 11) mg/kg/day for 8 weeks before and during gestation	Increased litter incidence of dilation of the lateral and/or third ventricle and subarachnoid space of the brain in pups gestationally exposed to ≥300 mg/kg-day	EPA identified 300 mg/kg-day (the lowest dose tested) as the LOAEL based on increased incidences of dilation of the subarachnoid space and dilation of the lateral and/or third ventricle of the brain in offspring; a NOAEL was not identified
Ema 2005 Drinking water	Species: Rat Administered doses: 0, 316, 1454, 5654 mg/kg/day on days 0–20 of Administered doses: 0, 316, 1454, 5654 mg/kg/day on days 0–20 of pregnancy (20/group)	No significant observations were noted in fetal brains, up to 5 g/kg-day, although developmental toxicity was noted	Based on the significant decreases in maternal body weight gain and fetal weight, it is concluded that the no observed adverse effect levels (NOAELs) of 1-butanol for both dams and fetuses are 1.0% (1454 mg/kg/day) in rats.
Nelson (1989a) Inhalation	Species: Rat Exposure route: inhalation Administered concentrations: 0, 3500, 6000, 8000 ppm (15/group) for 7 h/day on GD1-19	Enlarged brain ventricles observed in exposed fetuses but not significantly increased from control.	EPA identified the lowest concentration tested (11,000 mg/m^3 or 3,500 ppm) as a LOAEL based on the increased incidence of litters with skeletal variations; a NOAEL was not identified.
Nelson (1989b) Inhalation	Species: Rat Exposure route: inhalation Administered concentrations: 0, 3000, 6000 ppm (15 pregnant females/group) for 7 h/day throughout gestation; 0, 3000, 6000 ppm (18 males/group) for 7 h/day for 6 wks	No neurobehavioral effects in offspring, regardless of whether mothers or fathers exposed. Significantly higher levels of serotonin and dopamine in several brain regions (e.g. brain stem, midbrain).	EPA identified the highest concentration tested, 18,000 mg/m^3 (6,000 ppm) as a NOAEL based on a lack of neurobehavioral effects in offspring after parental inhalation exposure to n-butanol.
Hackett 1982 n-butyl acetate Inhalation	Species: Rabbit/Rat: Route: Inhalation Administered dose: 1500 ppm Group 1, none; Group 2, 7 to 16 gestation day (GD); Group 3, 1 to 16 GD; Group 4, pregestation, 1 to b 16 GD.	Rabbits: Reproductive performance was unaltered by n-butyl acetate exposure. Fetal effects of n-butyl acetate exposure included increased incidences of retinal folds, misaligned sternebrae, and	1500 ppm

		morphologic variations of the gallbladder in litters of rabbits exposed from 1 through 19 dg. No major malformations were observed. Rats: reduced food consumption, body weight and liver weight. Fetal size was reduced in all n-butyl-acetate exposed litters. Increased incidences of fetal rib dysmorphology in rats exposed from 7 through 16 dg, and more numerous hydroureters in fetuses from rats exposed prior to mating and from 1 through 16 dg. No evidence of teratogenic effect following exposure of rats to 1500 ppm.	

Health Assessment

The human studies provide reliable reports of ocular irritation that can be used for health assessment. On the low end of exposure, the Nelson (1943) study provides evidence of subjective assessment of n-butanol exposure that indicates 25 ppm causes uncomfortable effects in human after very short exposure (3-5 minutes). The study by Nelson does not report the experimental protocol, specifically the time between exposures, so it is not clear whether one test biased another due to lingering effects. The discrepancy between this report and that of the human study by Hempel-Jùrgensen (effect only at 990 ppm) may be that Hempel-Jùrgensen only considered eye redness and cytology as endpoints for irritation and there may be other sensory irritation effects that occur at lower doses. Kjaegaard provides support for this in that levels of irritation increased with n-butanol concentration and apparently in a linear fashion – average irritation doubled when n-butanol was raised from 1.5 to 3 ppm, even at this low concentration. The effects measured in Kjaegaard are qualitative and difficult to relate to clinical irritation. This is supported by the n-butanol only studies in Tabershaw where approximately 20 ppm was found acceptable for 8-hr exposure. Based on the human and workplace studies, there is some degree of irritation caused by n-butanol between the range of 25 and 100 ppm. 100 ppm and above is associated with ocular irritation in the workplace studies (Sterner, 1949).

The occupational studies are based on area sampling but those concentrations are within range of those producing effects in the human studies. The studies from Tabershaw are workplace investigation of eye inflammation from the 1940's and show some consistency with a NOAEL for irritation of 20 ppm. Additional detail from those studies are reported in the table below. Definitive irritation seems associated with concentrations above 20 ppm and more severe symptoms above 100 ppm. When butanol between 20 and 65 ppm, either as the sole solvent (study 4) or in a mixture (study 1), was removed from use, eye irritations ceased. These reports are not consistent with Sterner (1949) which was a prospective investigation spanning 10 years where no irritation as found at approximately 100 ppm.

From Tabershaw:

Plant	Butanol and other solvents	Observations
1	40 – 60 ppm 150 – 200 MEK	40 – "general concentration"; 60 - "spike" Irritation reports ceased after butanol removed.
2	5 – 14 ppm	After frequent complaints, relocation to a room with 5-14 ppm concentration caused irritation complaints to cease.
3	80 -100 ppm Naptha/ethyl alcohol (NR)	After switching from butanol to mixture, some cases of eye irritation still existed. Butanol after switch: 80 – 100 ppm
4	20- 65 ppm	5/30 reported eye irritation. When replaced with MEK, reports ceased.
5	60 – 115 ppm ethyl alcohol	Some cases of irritation; a few cases of headache/dizziness; many complaints of sickening odor.
6	15 – 100 ppm Denatured alcohol	75% butanol/25% denatured alcohol. 200 employees "appreciably" affected with eye inflammation. Cases greatest where butanol concentration highest.

Information on the health effects of humans from inhalation exposure to n-butanol consists of a few acute human exposure and occupational health studies. Controlled human exposure experiments have demonstrated that n-butanol vapors can exert an irritant effect on the eyes, nose, and throat under acute exposure conditions at air concentrations ≥10 mg/m3 (Kjaerguard et al., 1997; Nelson et al., 1943). Occupational health studies in which the primary exposure was to n-butanol reported effects including eye irritation (at 46–200 mg/m3) (Cogan et al., 1945; Tabershaw et al., 1944) and hearing loss (at 240 mg/m3) (Velazquez et al., 1969). Eye irritation is the most commonly observed effect in the workplace and controlled exposure experiments.

The animal toxicological database for inhalation exposure to n-butanol includes three subchronic exposure studies. (The primary toxicological effect observed in the subchronic exposure studies was a deficit in neurobehavioral performance. Korsak et al. (1994) reported a statistically significant increase in the failure rate for the rotorod test in rats exposed to 100 ppm n-butanol for 3 months. Decreased rotorod performance was used by EPA as the critical effect for its RfC derivation (EPA, DRAFT, YEAR). This measure was considered by EPA to be indicative of impaired neuromuscular function, relevant to humans and consistent with the alcohol and CNS literature (EPA ref). Performance deficits after 3 months were not significant at 50 ppm (though did increase during the exposure period). Selecting 50 ppm as the NOAEL, EPA conducted an interspecies extrapolation (i.e., rat-to-human) of n-butanol inhalation dosimetry using a rat and human PBPK model (Teeguarden 2005). This model does not calculate an internal dose metric for the brain so blood levels were used as the target endpoint in this analysis. A rat PBPK model was used to estimate the internal dose metric, calculated as the integral of the time profile for the arterial concentration of n-butanol corresponding to the NOAEL for decreased rotorod performance in a 6 hr/day 90-day rat study (Korsak et al., 1994). The human PBPK model was then used to estimate the continuous human inhalation exposure (mg/m3) that would result in the human equivalent arterial equivalent blood concentration. Through this conversion, the human equivalent $concentration_{cont}$ was determined to be 59 mg/m3 (19.21 ppm).

EPA applied a combined uncertainty factor of 1000 to this estimate based on the following uncertainties:

interspecies: 3 to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral n-butanol exposure. Use of PBPK modeling to convert the rat exposure concentration to a HEC

accounts for toxicokinetic differences between rats and humans but does not account for toxicodynamic differences between species..

intraspecies: 10 was applied to account for potentially susceptible individuals.

database: 3 was applied to account for database deficiencies. The toxicological database for inhaled n-butanol includes human experiments, occupational health studies, subchronic toxicity studies, and developmental and neurodevelopmental toxicity studies. The database lacks a multi-generation reproductive toxicity study.

subchronic to chronic: 10 was applied to account for extrapolation from a subchronic exposure duration study to a chronic RfC.

Applying these combined uncertainty factors (1000) to the RfC_{occ}

59 mg/m3/1000 = 0.059 mg/m3 (0.019 ppm)

This concentration can be scaled to an 8-hr occupational exposure limit by multiplying by 24/8 (hours) and 7/5 (days), resulting in an RfC_{occ} of 0.25 mg/m3 (0.08 ppm). The draft IRIS assessment of n-butanol was released for public comment in December 2011, but did not move forward to external peer review.

The other health effect observed in the subchronic study (David, 2001) was minimal to mild necrosis of the olfactory epithelium. The NOAEL for that effect was 500 ppm. The PBPK model cannot be used to calculate a human equivalent dose for olfactory necrosis because the model does not estimate a tissue dose for this compartment. The default dosimetric adjustment for contact site toxicity of a Category 1 vapor in the extrathoracic region is 1 so the human equivalent NOAEL is 500 ppm. Scaling the 6-hour exposure interval to 8 hours results in a POD of 400 ppm (6/8 x 500). An uncertainty factor of 300 for this study can be calculated as follows:

<u>interspecies:</u> 3 to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following n-butanol exposure. Using the Category 1 dose adjustment addresses toxicokinetic uncertainty. In addition, the measured blood/air partition coefficients in the rat and human for n-butanol are 1,160 and 677, respectively, suggesting a greater uptake per unit exposure in rats than humans so lowering this factor seems appropriate.
<u>intraspecies:</u> 10 was applied to account for potentially susceptible individuals.
<u>database:</u> 3 was applied to account for database deficiencies. The toxicological database for inhaled n-butanol includes human experiments, occupational health studies, subchronic toxicity studies, and developmental and neurodevelopmental toxicity studies. The database lacks a multi-generation reproductive toxicity study.
<u>subchronic to chronic:</u> 3 was applied to account for extrapolation from a subchronic exposure duration study to a chronic RfC. This uncertainty factored was lessened based on Sterner (1949) which reported no evidence of olfactory effects in workers exposed to 100 ppm over 10 years.

Applying this uncertainty factor to the POD (400 ppm/300 UF) yields an RfC_{occ} of 1.3 ppm.

RECOMMENDATION: A PEL of 20 ppm for n-butanol is proposed based on the findings in occupational investigations that concentrations below this value did not result in irritation or CNS effects in exposed workers. The CEILING notation is retained due to potential CNS effects. The SKIN notation for n-butanol is retained due to its moderate skin permeability

and wide-spread use as a solvent. Some Authoritative Bodies have removed the SKIN notation based on a calculation of systemic dose using a flux values of 0.019–0.048 mg cm2/hr (Scheuplein, 1973, from MAK documentation, see table in Appendix). Subsequent in –vitro studies have found substantially higher flux values for n-butanol (Boman, see table in Appendix).

CERS Usage information:

Pending

Measurement information

OSHA Method 7 (fully validated) uses a charcoal tube (or organic vapor monitor), a flowrate of 0.05 ppm, a volume range of 0.75 to 12 liters, and a GC-FID analytical method with an estimated detection limit of 23.5 picograms.

NIOSH Method 1401 uses a charcoal tube, a GC-FID, and provides an estimated detection limit of 0.01 mg per sample. Using the maximum sample volume of 10L this would result in an estimated detection limit of .1 ppm. The validated range studied was from 15 to 60 ppm.

Based on this information, there are no anticipated concerns with analytical feasibility to 20 ppm.

References

Bale AS,. Lee JS. 2016. An overview of butanol-induced developmental neurotoxicity and the potential mechanisms related to these observed effects. Neurotoxicology and Teratology 53 (2016) 33–40.

Cogan, DG; Mort, W; Grant, MD. (1945) An unusual type of keratitis associated with exposure to n-butyl alcohol (butanol). Arch Ophthalmol 33:106–108.

David RM, Tyler TR, Ouellette R, Faber WD, Banton MI, Garman RH, Gill MW, O'Donoghue JL. 1998. Evaluation of subchronic neurotoxicity of n-butyl acetate vapor.

David RM, Tyler TR, Ouellette R, Faber WD, Banton MI. 2001. Evaluation of subchronic toxicity of n-butyl acetate vapor. Food Chem Toxicol. 8:877-86.

ECHA, 2017. Scientific review on the link between the narcotic effects of solvents and (developmental) neurotoxicity Contract Number: ECA.6677-E3. March 2017 https://echa.europa.eu/documents/10162/13637/report_solvent_toxicity_final_en.pdf/d9b994f1-2f61-8a6f-2cca-d71e742ac10e

Ema M, Hara H, Matsumoto M, Hirose A, Kamata E. 2005. Evaluation of developmental toxicity of 1-butanol given to rats in drinking water throughout pregnancy. Food Chem Toxicol. 43:325-31.

USEPA, 2011 (Draft). TOXICOLOGICAL REVIEW OF n-BUTANOL (CAS No. 71-36-3). EPA/635/R-11/081A

Hackett-PL; Brown-MG; Buschbom-RL; Clark-ML; Miller-RA; Music-RL; Rowe-SE; Schirmer-RE; Sikov-MR 1982. Teratogenic study of ethylene and propylene oxide and n-butyl acetate. NIOSH 00133888. NTIS PB83-258038

Hempel-Jorgensen, A; Hudnell, HK; Kjaergaard, SK; et al. (1999) Time course of sensory eye irritation in humans exposed to n-butanol and 1-octene. Arch Environ Health 54(2):86–94.

Korsak Z, Wiśniewska-Knypl J, Swiercz R. 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int J Occup Med Environ Health.7:155-66.

McLaughlin J Jr, Marliac JP, Verrett MJ, Mutchler MK, Fitzhugh OG. 1964. Toxicity of Fourteen Volative Chemcials as Measured by the Chick Embryo Method. Am Ind Hyg Assoc J 25: 282-4

Nelson KW, Ege JF, Ross M, Woodman LE, and Silverman, L. 1943. Sensory Response to Certain Industrial Solvent Vapors Journal of Industrial Hygiene and Toxicology 25:282-285

Nelson BK, Brightwell WS, Khan A, Burg JR, Goad PT. 1989.
Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats.Fundam Appl Toxicol. 12(3):469-79

Nelson BK, Brightwell WS, Robertson SK, Khan A, Krieg EF Jr, Massari VJ. 1989. Behavioral teratology investigation of 1-butanol in rats. Neurotoxicol Teratol. 11:313-5.

NIOSH, 1992. Recommendations for Occupational Safety and Health, Compedium of Policy Statements and Documents. https://www.cdc.gov/niosh/docs/92-100/pdfs/92-100.pdf?id=10.26616/NIOSHPUB92100

Relation Between Local Eye Irritation Testing and Whole Body Irritation Response Using N-Butanol as a Model Substance. EPA/6001*A-97/014* PB97-193817

Sitarek K, Berlińska B, Barański B.1994. Assessment of the effect of n-butanol given to female rats in drinking water on fertility and prenatal development of their offspring. Int J Occup Med Environ Health. 7:365-70.

Sterner JH, Crouch HC, Brockmyre HF and Cusak M. 1949. A Ten-Year Study of Butyl Alcohol Exposure American Industrial Hygiene Assc Quaterly 10: 53-59.

Tabershaw, IR, Fahy, JP and Skinner, JB 1994. Industrial Exposure to Butanol 26:328-330.

Velazquez, J; Escobar, R; Almaraz, A. (1969) Audiologic impairment due to n-butyl alcohol exposition. In: Proceedings of the XVI International Congress on Occupational Health, Tokyo, Japan, 22-27 September 1969 Japan Industrial Safety Association.

APPENDIX

From n-butyl alcohol MAC documentation, https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb7136e5816

No data from humans are available at present for assessing absorption through the skin. Results from animal studies do not agree with data from in vitro studies using human skin. As regards their order of magnitude (0.019–0.048 mg cm^2 and hour), however, the latter agree with more recent data from animal studies with the isomeric compound *tert*-butyl alcohol (0.015 mg/cm^2 and hour; see supplement "tert-butyl alcohol" 2014). Taking the flux from in vitro investigations with human skin (0.048 mg/cm^2 and hour) as a basis, the absorption of 96 mg *n*-butyl alcohol, corresponding to 1.4 mg/kg body weight, is to be expected after the contact of both hands and forearms (area of skin 2000 cm^2) with undiluted *n*-butyl alcohol for one hour. Thus, for a diluted aqueous solution of *n*-butyl alcohol (concentration 0.1 M, flux 0.019 mg/cm^2 and hour) an absorbed amount of 38 mg or 0.54 mg/kg body weight would be obtained.

The MAK value for *n*-butyl alcohol of 100 ml/m^3 (300 mg/m^3) is based on the irritating effects of the substance. With regard to central nervous effects, a NOAEL of 125 mg/kg body weight was determined in a 90-day study with daily gavage administration to rats. Extrapolated to humans, a NOAEL of 22 mg/kg body weight (toxicokinetic correction, exposure for 7 days instead of 5, and the species-specific correction factor for the rat; see Section I of the List of MAK and BAT Values) would be obtained. Accordingly, both for undiluted *n*-butyl alcohol and for *n*-butyl alcohol in aqueous solution, dermal absorption is not expected to make any toxicologically relevant contribution to the systemic exposure. The compound is therefore not designated with an "H" (for substances which can be absorbed through the skin).

Gunnar Johanson, Matias Rauma, 2008. Basis for skin notation. Part 1. Dermal penetration data for substances on the Swedish OEL list. Report for Swedish Work Environment Authority.

Substance: Butanol, n-
CAS: 71-36-3
Scientific basis: AoH 1984:44

Skin notation: Yes
Skin permeability: Moderate

Molecular weight: 74.1
Density: 0.81 g/cm^3
Melting point: -89.5°C
Boiling point: 117.6°C
Vapour pressure: 0.7 kPa (at 20°C)
Evaporation rate: 0.46
Log Kow: 0.88

Reported data

Sp	Loc	Cell	L (µm)	A (cm^2)	V (ml)	Vehicle	C (mg/ml)	n	T_{Exp} (h)	T_{Obs} (h)	T_{Lag} (h)	Abs (%)	K_P (10^{-4} cm/h)	Flux (µg/cm^2/h)	Reference
In vitro															
Dog	Br	St	Full		1		*5%*	5	5	5			28	*111*	Mills et al. (2003)
Hum	Ab	St	26.6	2.5		*H2O*	*7.4*	8					25	*19*	Scheuplein et al. (1973)
Hum	Ab	St	2500	2.5		*H2O*	*7.4*	3					300	*220*	Scheuplein et al. (1973)
Hum	Ab	St	26.6	2.5			Neat	7					0.6	*48*	Scheuplein et al. (1973)
Hum	Ab	St	2500	2.5			Neat	8					10	*820*	Scheuplein et al. (1973)
Hum		Fl	250	1	0.2-0.3		Neat	3	24	24		*1.8 (9h)*	*4.1-6.2*	*330-500*	Boman et al. (2000)
Hum		Fl	250	1	0.2-0.3	Tol	50%	5	21	21		*70 (10h)*	*140-200*	*5600-8400*	Boman et al. (2000)
Hum		Fl	250	1	0.2-0.3	Chf + Me	50%	6	21	21		*22*	*21-32*	*840-1300*	Boman et al. (2000)