

**Substance name: n-butyl acetate**

CAS: 123-86-4

MW: 116.16 gm/mole

Synonyms: butyl acetate; 1-butyl acetate; acetic acid; n-butyl ester; butyl ethanolate

Molecular formula: C<sub>6</sub>H<sub>12</sub>O<sub>2</sub>

Structural formula (image to right):

Conversion factor: (at 20 °C, 760 mm/Hg) 1 ppm = 4.83 mg/m<sup>3</sup>

Physical characteristics at room temp:

boiling point 259 °F

melting point -107 °F

vapor pressure 10 mmHg

solubility 7 gm/l

density 0.88 gm/cm<sup>3</sup>Log P<sub>ow</sub> 1.82

Special physical characteristics if any:

colorless with fruity odor

Flammability and other hazards:

flash point 75 °F (closed cup); 99 °F (open cup)

Major commercial form(s):

It is usually found in as a component in a solvent mixture.

Uses/applications:

Estimated uses: nitrocellulose-based lacquers 63%, exports 27%, ink solvent 5%, adhesives solvent 2%, and other solvent uses 3%. As a lacquer solvent it is used in wooden furniture and auto top-coat applications. Other uses may include solvent in the production of airplane dopes, extraction solvent in the manufacture of penicillin, synthetic flavoring ingredient used in producing banana, pear, pineapple and berry flavors, solvent for fats, waxes, camphor, gums, resins, lacquer stains, ester-soluble dyes and cellulose esters. In commercial grade it has been used in the manufacturing of vinyl resins, and preservation of foodstuffs. Other reported uses include photographic film manufacturing, in nail polish removers, other products for manicure, and as a flavoring agent in the cosmetics industry. It occurs naturally in bananas and other related fruits, and it is created during fermentation processes.

Odor Thresholds:

Detection: 0.31 ppm; Recognition: 0.68 ppm (AIHA 1997).

Metabolism:

N-butyl acetate is readily absorbed via inhalation and oral exposure. It is readily hydrolyzed to acetic acid and n-butanol, the major metabolite. An estimated 10-20% is metabolized in the respiratory tract. After inhalation of low concentrations, approximately 50% was found in exhaled air unchanged. The half-life of n-butyl acetate in human blood (in vitro) is approximately four minutes (Essig et al 1989). Pharmacokinetic modeling estimated human inhalation exposure to 190 ppm results in approximately the same n-butanol blood concentration as rats inhaling 100 ppm.

**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 150 ppm; STEL 200 ppm		
NIOSH REL (1992)	TWA 150 ppm; STEL 200 ppm		

ACGIH TLV (2015)	TWA 50 ppm; STEL 150 ppm	Eye and upper respiratory tract irritation.	
MAK (current)	TWA 100 ppm		
Washington State OSHA	TWA 150 ppm; STEL 200 ppm		
ECHA (REACH) Derived No Effect Level (DNEL) = 12 mg/m <sup>3</sup> and 102.34 mg/m <sup>3</sup> .	Subchronic; male and female Sprague-Dawley rats (15 animals/sex/dose group) were exposed to nominal concentrations of 0, 500, 1500 or 3000 ppm of <i>n</i> -butyl acetate for 6 hours per day, 5 days per week for 13 consecutive weeks. The time-weighted average analytical concentrations were within 10% of the target concentrations.	These values are based on the same key study and NOAEC; however, the overall assessment factor (AF) applied are 50 and 1, respectively. NOAEC: 500 ppm Critical effect: no systemic or organ-specific toxicity.	

### Peer-reviewed journal articles and other studies

Author	Study type	Results	Discussion and Assessment
Flury, 1933	The irritating potential of <i>n</i> -butyl acetate via inhalation was tested at concentrations of 210 and 2,100 ppm in 2–4 test persons. The subjects were exposed for 5 min in an inhalation chamber, 3 min after spraying and evenly distributing <i>n</i> -butyl acetate.	Noted effects of <i>n</i> -butyl acetate were irritation to the eyes, nose, throat and esophagus, reportedly weak at 210 ppm and moderate at 2,100 ppm.	The authors observed customization over time.
Nelson 1943	10 healthy volunteers were exposed to <i>n</i> -butyl acetate for 3–5 min. The test persons themselves subjectively scored the extent of irritation (none, weak, severe).	At 200 ppm, irritation of the throat was reported, while irritating effects on eyes and nose occurred at 300 ppm. At this concentration, the effect on the throat was already considered severe.	
Iregren 1993, Part I	The irritating potential of <i>n</i> -butyl acetate was tested in 24 non-smoking, not occupationally exposed volunteers in a series of three different chamber studies. The first group of volunteers (n = 24, experiment I) was exposed to concentrations of 72.5, 145, 220 and 290 ppm. Exposure lasted 20 minutes and was repeated four times in intervals of 24 hours. In this experiment, the following effect measures were employed: magnitude estimation of irritation, category scales of irritations (eyes, nose, throat, skin, breathing difficulties, sensation of bad smell) and category scales of CNS effects (headache, vertigo, nausea, tiredness).	Under these conditions, subjects reported irritation to the throat, difficulties in breathing and a sensation of a bad smell. The trends towards increasing effects with increasing exposure level were only weak and there were no significant differences in effect size between any of the exposure concentrations and the baseline level before exposure.	The psychophysical function relating total perceived irritation in this experiment did fit very well with empirical data (R <sup>2</sup> = 0.999).

Iregren 1993, Part II	In the second experiment, volunteers (n = 23) were exposed to 14.5 (as “control” level) 290 ppm <i>n</i> -butyl acetate twice for 20 min at intervals of 7 hours. In this experiment, measurements of pulmonary function (respiratory frequency, total lung capacity, airway resistance, forced expiratory volume, vital capacity, forced vital capacity, maximal expiratory flow, specific airway resistance, closing volume) and eye irritation (blinking frequency, eye redness, lipid layer thickness, tear film break up time, conjunctival epithelial damage) were done besides scaling of CNS effects and irritation.	In this test (experiment II), ratings for irritation of all sites except skin differed significantly between 290 ppm and the control. No substantial effects on the lipid layer of the eyes were observed after the 20 min exposures. Yet, after experiment II, bronchial responsiveness was significantly increased after 20 min exposure to 290 ppm of <i>n</i> -butyl acetate.	
Iregren 1993, Part III	In the third part of the study (experiment III), 12 subjects were exposed to 14.5 (control) and 145 ppm of <i>n</i> -butyl acetate twice for 4 hours within 7 days.	Significant effects at 145 ppm were observed for throat irritation, difficulties in breathing and sensation of a bad smell, but no effect on ocular irritation. The results of pulmonary function measures were quite similar to experiment II. Eye redness was increased in 50% of the subjects following exposure to 145 ppm as compared to 17% during control conditions. Bronchial responsiveness was significantly increased at 145 ppm.	For the item “bad smell” there was a decreasing rating during the exposure time. The authors of the study concluded a rather low irritating potential of <i>n</i> -butyl acetate.  Altogether, the 3 experiments have some weaknesses as the lowest exposures to <i>n</i> -butyl-acetate were obviously too high to serve as control conditions.
(Osterberg 2000, and Osterberg et al 2003)	Another study exposed subjects for 3-5 minutes, and those exposed to 200 ppm reported throat irritation. Those exposed to 300 ppm also reported eye and nose irritation (throat irritation considered severe). Another study involved 20-minute exposures repeated four times in 24 hours to 72.5, 145, 220 and 290 ppm and examined irritation to eyes, nose, throat, skin, breathing difficulties, sensation of bad smell, and scales of CNS effects (headache, vertigo, nausea, tiredness).	Subjects reported irritation to the throat, difficulties breathing and a sensation of a bad smell. The trends toward increasing effects with increasing exposure were only weak and there were no significant differences in effect size between any of the exposure concentrations and baseline. Another study involved patients with toxic encephalopathy with subjective hypersensitivity to chemicals who were exposed up to 11 ppm <i>n</i> -butyl acetate for two hours and did not show dose-related changes in neurological performance testing.	
Abraham 1996	Anosmic patients were exposed to <i>n</i> -butyl acetate for 2 seconds.	A threshold value of 3,650 ppm for nasal irritation was identified.	The finding suggests an important influence of the smell on the subjective sensation of irritation.

Caron, 2010	Inhalation challenges are used for diagnosing occupational asthma. The initial methodology consisted of a "realistic" exposure without monitoring nor controlling exposure. Forty-four different subjects to a control agent (n-butyl acetate) and/or to a suspected occupational agent.	Nineteen of the subjects were only exposed to N-Bu acetate as a control agent without experiencing any significant irritant effect (no significant changes in spirometry thereafter). Eight subjects who were exposed to both N-Bu acetate and formaldehyde did not show significant reactions.	The exposure concentration not available.
Greim 1999	No irritating or sensitizing effects on the skin were observed after dermal exposure to 4% <i>n</i> -butyl acetate in petrolatum as well as after repeated exposure to nail polish containing 25.5% <i>n</i> -butyl acetate. The same results were obtained after repeated insult patch testing (9 × 24 hours within 3 weeks) with 0.5 ml pure liquid.	Only one person who was occupationally exposed to <i>n</i> -butyl acetate and one patient suffering from dermatitis showed positive results.	Because sensitization tests were negative in all other test persons, <i>n</i> -butyl acetate seems to have no relevant skin sensitizing potential.
Alarie 1998	The RD50 (concentration causing a 50% depression of the respiratory rate due to sensory irritation of the respiratory tract) of <i>n</i> -butyl acetate was 733 ppm in Swiss OF1 mice.		
David 1998	In a subchronic inhalation study, the neurotoxicity of <i>n</i> -butyl acetate at concentrations of 0, 500, 1,500 and 3,000 ppm (6 hours/day, 5 days/week) was tested in both food-restricted (13 weeks) and <i>ad libitum</i> fed rats (14 weeks). Endpoints for neurotoxicity testing were a functional observed battery (FOB), motor activity, neurohistopathology ( <i>ad libitum</i> fed rats) and schedule-controlled operant behavior (SCOB, food-restricted rats). During the experiment, no spontaneous mortality occurred in any of the groups.	The only sign of systemic toxicity was a significantly reduced body weight in the <i>ad libitum</i> fed rats at concentrations of 1,500 and 3,000 ppm <i>n</i> -butyl acetate. No treatment-related histopathological effects were detected. At 3,000 ppm and beginning on the second day also at 1,500 ppm, rats were less active and movement and response to stimuli were slowed down (both feeding groups). No signs of neurobehavioural effects and no systemic toxicity were determined 30–60 min after cessation of exposure.	Besides the described transient effects of sedation and hypoactivity, there was no evidence of neurotoxicity.
David 2001	In a second study with analogous experimental design (all rats fed <i>ad libitum</i> ), <i>n</i> -butyl acetate vapor equally led to reduced activity levels and decreased body weights at concentrations of 1,500 and 3,000 ppm.	Due to the body weight loss, the organ weights of liver and kidney were reduced, but no systemic or organ specific toxicity was noted. Hematocrit, hemoglobin and erythrocyte counts, while still in the normal range, were increased compared to controls. At <1,500 ppm, necrosis of the olfactory epithelium along the dorsal medial meatus was detected. The severity of the olfactory	

		lesions was dose dependent. At 3,000 ppm, signs of irritation of the glandular stomach and necrosis of the non-glandular stomach were reported in females. No effects were observed at 500 ppm (NOAEC).	
(Rim, 2015)	Micronucleus (MN) assay of <i>n</i> -butyl acetate using male Institute for Cancer Research (ICR) mice bone marrow cells. The seven-week-old male ICR mice were tested at three dosages for this chemical. 24 hr of oral administration.	No increase the incidence of micronuclei. Not classified as a mutagen in the globally harmonized system of classification and labelling of chemicals.	As the result of counting the micronucleated polychromatic erythrocyte (MNPCE) of 2,000 polychromatic erythrocytes, the <i>n</i> -butyl acetate did not inhibit the bone marrow cell proliferation in all treated groups, and did not increase the occurrence of MN.
Hackett <i>et al</i> 1983	In a reproductive toxicity study, rats (n = 40) and rabbits (n = 30, artificially inseminated) were exposed to <i>n</i> -butyl acetate at 1,500 ppm for several days during gestation (7 hours/day). Of the rats, group 1 was exposed to filtered air (control), group 2 was exposed to <i>n</i> -butyl acetate on gd 7–16, group 3 on gd 1–16 and group 4 was exposed on 5 days per week for 3 weeks prior to mating and again on gd 1–6. Rabbits were exposed to filtered air (control, group I) or to <i>n</i> -butyl acetate either on gd 1–19 (Group II) or on gd 7–19 (Group III).	Maternal toxicity was observed in all exposed animals, manifest in reduced food consumption (rats and rabbits) and reduced body weights (rats). No malformations, increased numbers of resorptions or deaths occurred in rabbits in any of the exposed groups. The incidences of some morphologic variations were increased in rabbits of group III. In rats, signs of minor developmental toxicity were detected. Fetal growth (crown-rump length, body weight) was reduced in all exposure groups, which could be due to the observed reduced body weight of the dams. Reduced pelvic ossification occurred in fetuses of groups 2 and 3 and dilated ureters occurred in group 4. The only significant fetal effect of <i>n</i> -butyl acetate was an increase in the incidence of rib dysmorphology in rats (wavy, fused and bifid ribs). This effect was found in all exposed groups of rats.	Because the observed findings were only variations and no malformations, the authors concluded that they were not due to teratogenic effects. Furthermore, the detected developmental effects might be due to the maternal toxicity.
(Saillenfait, 2007) Part 1	The developmental toxic potential of <i>n</i> -butyl acetate (BA) was examined in Sprague-Dawley rats following whole body inhalation exposure, 6 h day (-1), from day 6 to 20 of gestation, at concentrations of 0, 500, 1000, 2000 and 3000 ppm.	Maternal significant decreases in body weight gain at 2000 and 3000 ppm and reduced food consumption at 1000 ppm and higher concentrations. Prenatal development limited to a significant decrease in fetal weight at 3000 ppm.	<i>n</i> -butyl acetate not a selective developmental toxicant.
(Saillenfait, 2007) Part 2	Second part of study, the developmental toxic effects of	The maternal weight gain was reduced after exposure to	A significant reduction of fetal weight was associated with

	simultaneous exposures to ethylbenzene (EB) and BA, or to toluene (TOL) and BA were evaluated. Pregnant rats were administered EB (0, 250 or 1000 ppm) and BA (0, 500 or 1500 ppm), or TOL (0, 500 or 1500 ppm) and BA (0, 500, 1500 ppm), separately and in combinations, using a 2 x 2 factorial design.	1000 ppm ethylbenzene (EB), to 1500 ppm n-butyl acetate (BA), or to 1500 ppm toluene (TOL), either alone or in binary combinations. There was no evidence of interaction between EB and BA or between TOL and BA in causing maternal or developmental effects.	exposure to 1000 ppm EB alone, to either mixtures of EB with BA, or to 1500 ppm TOL alone or combined with BA at either concentration. No embryo-lethal or teratogenic effects were observed whatever the exposure.
Nelson 1989	The developmental toxicity of <i>n</i> -butanol, the major metabolite of <i>n</i> -butyl acetate, was investigated. In this study, rats were exposed to 0, 3,500, 6,000 and 8,000 ppm <i>n</i> -butanol on gd 1–19 for 7 hours per day.	Fetal body weights were reduced at $\geq 6,000$ ppm. At 8,000 ppm, the incidence of skeletal alterations was increased. For <i>n</i> -butanol, no effects were observed at 3,500 ppm.	
David 2001	Reproductive study with 13-week inhalation study in rats.	No dose-related effects on the epididymal or testicular sperm count.	

### **Other Studies**

**Skin Absorption:** reported to be absorbed epicutaneously by humans (Spasovski and Bencev 1971), however, a low permeability constant ( $1.6 \pm 0.1$  g/m<sup>2</sup>/hour) was reported in living human skin (Ursin 1995). And the acute toxicity of *n*-butyl acetate is considerably lower after dermal exposure than after oral exposure. Thus, no “skin” notation is proposed.

**Genotoxicity Summary:** *n*-butyl acetate showed no genotoxic effects in *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537) at concentrations of 33–10 000 µg/plate (Zeiger *et al* 1992) and in *Escherichia coli* (Shimizu 1985) both with and without activation. Negative results were obtained at all tested concentrations in a yeast assay (D61.M) and after incubation of Chinese hamster lung (CHL) cells. Negative results were obtained in all tested concentrations in the micronucleus assay in seven-week-old male ICR mice (Rim 2015).

The comparison of the sensory NOAEC human with the irritative NOAEC animal (chronic) resulted in an interspecies extrapolation factor of 3 for extrapolating animal data concerning local sensory irritating effects. The adequacy of this was confirmed by its application to additional substances with lower data density (acetaldehyde, ammonia, *n*-butyl acetate, hydrogen sulfide, and 2-ethylhexanol). Thus, extrapolating from animal studies, uncertainty factor of 3 should be applied for local sensory irritants without reliable human data, unless individual data argue for a substance-specific approach (Bruning, 2014).

### **HEAC Health-based Assessment and Recommendation**

Rodent short-term, i.e. 4-hour, inhalation studies found LC50 values above 4,000 ppm in rats and 1,260 ppm in mice. Effects included irritation to eyes, nose and respiratory tract. At higher exposures, effects included severe damage to the lung (haemorrhagia, edema, and congestion), which is the main cause of death, as well as central nervous effects leading to narcosis. Exposures to mice and cats at 6,210 and 6,830 ppm respectively caused anesthesia.

The effect concentrations obtained in several human studies on acute irritation after inhalation exposure to *n*-butyl acetate were inconsistent, possibly due to the differences in study design, subjective reporting

or other unknown reasons. Nelson et al (1943) observed mild or moderate irritating effects (throat or eyes, nose, throat and esophagus) after inhalation of 200 ppm (966 g/m<sup>3</sup>) for 3–5 min. The extent of irritation was scored subjectively based on three categories: not, slightly and very. Also, dose-effect relationships at higher concentrations are contradictory. Flury and Wirth (1933) found “moderate” irritation effects after inhalation of 2,100 ppm for 5 min, whereas Nelson et al (1943) reported “severe” throat irritation at 300 ppm for 3–5 min. Despite these discrepancies, from the overall evidence of these human studies, n-butyl acetate is expected to cause airway irritation at  $\geq 200$  ppm after short term (5–20 min) exposure. In contrast, Iregren et al (1993) observed only minimal effects in the throat after exposure to up to 290 ppm, which were not significantly different from the control values after 20 min of exposure. However, after 4 hours of exposure, throat irritation and breathing difficulties occurred already at 145 ppm and eye redness was found in 6 persons. Also, bronchial responsiveness was significantly increased. In this experimental study, the proposed “control exposure levels” of 14.5 and 74.5 ppm, respectively, were probably too high to set a zero point for scaling and statistical analysis.

No neurotoxicity or other systemic effects were observed in a rodent study at 500 ppm (NOAEC), with only marginal neurotoxicity (decreased activity) and unspecific effects (hematological changes within normal range and reduced weight) at 1,500 ppm (David 2001).

#### Overall assessment

Regarding the critical effect irritation in humans, the LOAEC of 150 ppm (700 mg/m<sup>3</sup>) in the study by Iregren et al (1993) is the starting point for recommending an OEL. Due to the exposure duration of 4 hours, a safety factor of 3 is justified for deriving a recommended OEL. An OEL of 50 ppm (240 mg/m<sup>3</sup>) is proposed for n-butyl acetate to protect workers against systemic and local toxic effects during an 8-hour exposure.

A STEL of 150 ppm is recommended to avoid possible irritating effects reported in case and human exposure studies. n-Butyl acetate was not sensitizing to the skin after dermal exposure of either humans or animals, nor is the permeability through human skin high enough to warrant a ‘skin’ notation.

#### **CERS Usage information:**

SIC Code	Butyl Acetate Users in CERS (n)			
	Average Daily Amount (gal)			
	n-	isobutyl	tert-	sec-
	(130)	(9)	(108)	(1)
10-19	23.7	-	161.8	-
20-29	46.6	-	849.0	-
30-39	33.8	1.2	159.6	0.03
40-49		-	232.7	-
50-59	12423.1	5782.7	1651.1	-
70-79	29.4	-	46.1	-
80-99	4.5	5.3	0.4	-

#### **Measurement information**

OSHA Method 1009 (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 1450 uses a charcoal tube (or organic vapor monitor), a GC-FID, and provides an estimated detection limit of 0.9 µg.

#### Works Cited

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