

WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL[®]



Butyraldehyde (2016)

I. IDENTIFICATION⁽¹⁻¹⁴⁾

Chemical Name: Butyraldehyde

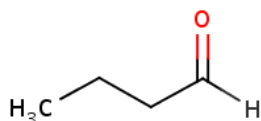
Synonyms: Butal; butaldehyde, butalyde, butanal, butanaldehyde, butyl aldehyde, butyral, butyric aldehyde

CAS Number: 123-72-8

DOT/UN Number: 1129

Molecular Formula: C₄H₈O

Structural Formula: CH₃CH₂CH₂CHO



II. CHEMICAL AND PHYSICAL PROPERTIES⁽¹⁻¹³⁾

Physical State: colorless liquid (at room temperature)

Molecular Weight: 72.1

Conversion Factors: 1 mg/m³ = 0.34 ppm

1 ppm = 2.95 mg/m³ @ 25 °C and

760 mmHg Melting Point: -80 °C (-112 °F)

Boiling Pt: 74.8 °C (167 °F) at 760 mm Hg

Vapor Pressure: 88 to 92 mm Hg at 20 °C (68 °F)

Saturated Vapor Concentration: 1.16 × 10⁵ to 1.21 × 10⁵ ppm at 20 °C (68 °F)

Vapor Density (air =1): 2.5

Odor description: characteristic pungent, aldehyde odor

Odor threshold: low = 0.136 mg/m³ (0.005 ppm); high = 26.55 mg/m³ (9.0 ppm)

Flammability Limits: LFL – 1.9%, UFL – 12.5%

Flash Point (closed cup): -12 to -7 °C (10 to 20 °F)

Autoignition temperature: 230 °C (446 °F)

Specific Gravity: 0.80 at 20 °C (68 °F)

Solubility in Water: 7.1 % by weight at 25 °C (77 °F)

Soluble in alcohol, ether, acetone and benzene

Stability and reactivity: Stable. Reactive with caustic soda, organic acids, ammonia, alcohols, and halogenated compounds. Readily oxidizes in air to form butyric acid. Oxidizing material can cause a vigorous reaction.⁽⁹⁾ It is one of the major degradation products of polyvinylbutyral paint⁽¹⁰⁾ and a moderate degradation product of epoxy, ethyl silicate, and latex paints.⁽¹¹⁾

III. USES⁽¹⁵⁻¹⁹⁾

Butyraldehyde is used chiefly in the manufacture of rubber accelerators, synthetic resins, solvents and plasticizers. It is used

as a synthetic flavoring agent in foods such as alcoholic and non-alcoholic beverages, ice cream, candy and baked goods. It is considered as “generally recognized as safe” as a food additive by the FDA and was listed by the Council of Europe (1974) with an ADI of 1 mg/kg. The 1992 to 1995 production volumes in the U.S. are listed as between 1.88 to 2.68 × 10⁹ pounds.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

Species	Route	LD ₅₀ Or LC ₅₀
Mouse	Inhalation	44,610 mg/m ³ (15,167 ppm) ^(15,16,19,20)
Mouse	Intraperitoneal	1.14 g/kg ⁽¹⁶⁾
Mouse	Subcutaneous	6.17 g/kg anesthesia, hemoglobinuria ⁽²¹⁾
Guinea Pig	Skin	>20 g/kg ^(9,16,19)
Rabbit	Skin	1.0-2.8 g/kg (24 hour occluded) ⁽²¹⁾
Rat	Oral	2.5-5.9 g/kg ⁽¹⁶⁻²²⁾
Rat	Inhalation	16,400 ppm ^(15,16,19,20)
Rat	Inhalation	59,160 ppm anesthesia effect ^(15,16,19,20)
Rat	Intraperitoneal	0.8 g/kg ⁽²²⁾
Rat	Subcutaneous	10 g/kg anesthesia, hemoglobinuria ⁽²¹⁾

Antagonistic acute toxicity has been demonstrated with acrolein, methyl vinyl ketone, acetonitrile and p-nitroso-n,n-dimethylaniline; additive toxicity shown with acrylamide and ethylene chlorohydrin; and synergistic toxicity with glutardialdehyde.

2. Eye Irritation^(9,23-26)

A volume of 0.005 mL of a 15% solution instilled into the eyes of rabbits produced moderate to severe corneal injury with iritis.

A volume of 0.02 mL of neat material instilled into the eyes of rabbits produced moderate to severe corneal injury with iritis and 0.005 mL (neat) produced trace to moderate corneal injury.

3. Skin Absorption

No data is available other than lethality listed above.

4. Skin Irritation

A volume of 0.01 mL of neat material applied on uncovered, clipped intact skin of rabbits for 4 hr produced minor irritation in two of five rabbits and no effect in the remaining three.⁽²³⁾

Application to occluded intact or abraded skin (volume not provided) for 24 hr produced severe irritation.⁽¹⁶⁾ Moderate dermal irritation (methods not provided) was reported following application to guinea pigs.^(9,15,16)

5. Skin Sensitization

Butyraldehyde was negative in a guinea pig sensitization test using 8 animals (4/sex).⁽²⁶⁾

6. Inhalation Toxicity

An RD_{50} (50% decreased respiratory rate) of 5572 ppm was determined for the rat (F-344).^(15,16,19,20)

B. Subacute Toxicity

Rats (numbers/strain not indicated) exposed by inhalation to butyraldehyde at a high dose of 2710 mg/m³ (934 ppm) for 6 hours/day, 5 days/week for 20 exposures had oral discharge and increased adrenal and lung weights; however, no effects were seen at 930 mg/m³ (320 ppm).⁽¹⁵⁾

Rats (three males and four females) exposed by inhalation 6 hr/day, 5 day/week for 12 exposures to 1000 ppm butyraldehyde exhibited no clinical signs and organs were normal at necropsy. Histological evaluation of the lungs and several abdominal organs found no toxic response.⁽²⁷⁻³¹⁾

Rats (5/sex/dose), mice (5 male/dose), guinea pigs (3 male/dose), rabbits (1/dose sex, not indicated) and dogs (1 male/dose) were exposed to mean butyraldehyde concentrations of 0, 2000, 3100 or 6400 ppm for 6 hr/day 5 days/week for nine days. All animals died in the 6400 ppm group except one rat. Signs of ocular and respiratory irritation, loss of coordination and anesthesia generally occurred in all animals prior to death. The one beagle in the 3100 ppm group died after the third exposure. There were no other mortalities. Clinical signs of ocular and nasal irritation occurred in both the 2000 and 3100 ppm group. At 3100 ppm the body weights for all species were decreased; body weights were generally not affected for the 2000 ppm group while most other values for the 3100 ppm group were abnormal. There were no gross lesions in animals of the 2000 or 3100 ppm groups. No histological evaluations were conducted for this study.⁽²⁷⁻³¹⁾

Rats (ten female and ten male Sprague-Dawley) were exposed to 293, 930 and 2710 mg/m³ (20 each sex as controls) for 4 weeks (6 hrs/day, 5 days/week). No mortality occurred in any treatment of control animals. Observations of treated animals indicated a red or clear oral discharge in some animals. Weight gain was normal for all groups and there were no significant

changes to hematology, clinical chemistry or urinalysis parameters. Adrenal/body weight and adrenal/brain weight ratios were statistically elevated in the high-dose male group. Lung/body weight and lung/brain weight ratios were statistically elevated in both male and female rats in the high-dose group. However, there was no gross or microscopic pathology findings.⁽³²⁾

C. Subchronic Toxicity

Male and female rats treated by gavage with 0, 0.075, 0.15, 0.3, 0.6 or 1.2g of butyraldehyde /kg 5 day/wk, for 13 weeks displayed a dose-related increase in mortality and decrease in body weight with an increased incidence of irritation, inflammation, necrosis, hyperplasia and lesions in the forestomach and gastric mucosa with 100% of males and 90% of females affected at the high-dose group.⁽¹⁵⁾

Rats and dogs (numbers not specified) exposed by inhalation to 0, 125, 500 or 2000 ppm 6 hrs/day 5 days/week for 13 weeks displayed decreased alkaline phosphatase (500 ppm) and decreased RBC and monocyte counts (125 ppm) and lesions of the nasal epithelium and pneumonia (125 ppm). Dogs had elevated levels of albumin (125 ppm) and nasal mucosal lesions (500 ppm).⁽¹⁵⁾

Twenty Sprague-Dawley rats/sex and 4 male beagles per group were exposed to mean butyraldehyde concentrations of 117, 462 or 1852 ppm for 6-hr/day, 5 days/week for 13-14 weeks. Clinical signs of ocular and upper respiratory tract irritation occurred at all exposure concentrations. No exposure-related effects occurred on body-weight, serum chemistry, hematology, urine analysis, or liver or kidney weights for rats or dogs. No abnormal ophthalmic findings were recorded for rats, while one dog in the 462 ppm group and all dogs in the 1852 ppm group had slight conjunctivitis. Histopathological changes in dogs in the 1852 ppm group included marked rhinitis with mucosal cell hyperplasia, inflammation, and squamous metaplasia. Squamous metaplasia also occurred in the larynx and trachea in one dog of this group. Dogs in the 117 and 462 ppm groups had goblet cell hyperplasia in the nasal mucosa. Histopathological changes in rats included mild to severe rhinitis and mild to severe squamous cell metaplasia of the respiratory epithelium in all three butyraldehyde exposed groups with the incidence and severity generally decreasing with decreasing exposure concentration. Goblet cell hyperplasia of the nasal epithelium generally occurred in rats in the 117 and 462 ppm groups; atrophy of the goblet cells occurred in the 1852 ppm group. Specifically for animals of the 117 ppm group, goblet cell hyperplasia was observed in three of four dogs; mild to moderate rhinitis was observed in 30% of the rats; most rats had mild squamous metaplasia but 20% were graded as moderate to marked. There were no exposure-related histopathological lesions found in the lungs or testes of dogs or rats exposed to butyraldehyde.⁽³³⁻³⁶⁾

For 6 hr/day, 5 days/week for 13 weeks, 15 F-344 rats/sex/group were exposed to mean butyraldehyde concentrations of 1, 10 or 51 ppm. There were no exposure-related effects on body weight, serum chemistries, kidney or

liver weights, ophthalmic or neurological examinations, or histological evaluations.⁽³⁷⁾

For 5 days/week for 90 days, 10 F-344 rats and B6C3F1 mice/sex/group were gavaged with 75, 150, 300, 600 or 1200 mg/kg butyraldehyde in corn oil. Nasal discharge, rales, ruffled fur, and urine stains were observed in rats of the 600 and 1200 mg/kg groups. All rats of the 1200 mg/kg group died during the study. Although many deaths occurred in the other groups, it was concluded that they were the result of gavage errors. Some exposure-related deaths also occurred in the 1200 mg/kg group of mice. There were decreased body weights (rats) or body weight gain (mice) in the 1200 mg/kg group; decreased body weight occurred in the 300 mg/kg group male rats and the 600 mg/kg group female rats. Histopathological evaluation defined the stomach and the nasal cavity as the principal target organs. Lesions in the stomach included inflammation, erosion, ulceration, necrosis, hyperplasia and hemorrhage, which probably resulted from direct toxicity to the mucosal epithelium from the butyraldehyde. Inflammation of the nasal cavity was thought to have resulted from the reflux of the compound when animals were gavaged. The no-effect levels were 300 mg/kg for mice of both sexes and female rats and 150 mg/kg for the male rats.^(38,39)

D. Chronic Toxicity and Carcinogenicity

Evidence for the potential carcinogenicity of butyraldehyde is inconclusive.^(7,8)

E. Reproductive/Developmental Toxicity

In one study a single intraperitoneal (i.p.) dose of 1 mg butyraldehyde/mouse produced sperm abnormalities (motility/morphology), which were present one month post-dosing. In another study similar abnormalities were seen with: exposure to 0.2 g/L of butyraldehyde in drinking water for 1 month; a single i.p. dose of 30 mg/kg (at 0.2 mg/L); and exposure to 300 mg/kg/day in water for 50 days. In both reports, chromosomal and meiotic anomalies were observed at all stages of spermatogenesis; however, the numbers of test animals and mouse strains were not provided in either report.^(8,15,40,41)

A subsequent 90-day oral NTP study in mice and rats (150–600 mg/kg bw mice, and 75–300 mg/kg bw rats by gavage) indicated no significant effects on sperm motility, caudal, epididymal or testicular weights or on the estrous cycle of females.⁽⁴²⁾

F. Genotoxicity/Mutagenicity

1. *In vitro*

Tests in *Salmonella typhimurium* TA98, TA100, TA1535 or TA 1537 either with or without microsomal enzymes were negative.^(43–45) Equivocal results were obtained in *Drosophila melanogaster* when evaluated for sex-linked recessive lethality.^(46–48) Butyraldehyde was not mutagenic in *Escherichia coli* when tested for reversion from streptomycin

dependence.⁽⁴⁹⁾ It is not been shown to induced sister chromatid exchanges (SCE) in human lymphocytes treated *in vitro* for 24 and 48 hours^(49,50) and was negative in inducing DNA repair synthesis (UDS) in human and rat hepatocyte primary cultures.⁽⁵¹⁾

2. *In vivo*

In Chinese hamster V79 cells, butyraldehyde induced a dose-dependent increase in the frequency over controls of both 6-thioguanine and ouabain resistant mutants at concentrations of 0, 1, 3, 10, and 30 mM. Butyraldehyde was shown to cause a dose-dependent decrease in survival of rat and human hepatocytes using the trypan-blue exclusion test. Extrapolating these results to *in vivo* conditions was considered, however, to be problematic.^(52,53)

G. Metabolism/Pharmacokinetics

Aliphatic aldehydes (e.g. butyraldehyde) are expected to be metabolized rapidly to the corresponding acid by normal endogenous pathways. Absorption is via oral and inhalation routes and excretion of similar chemicals has involved glutathione conjugation.⁽¹⁵⁾

H. Other

Neurotoxicity: Anesthesia occurs in rats exposed by inhalation to undefined high levels. Dose-related reductions in amplitude and decreased conduction velocity were observed in *in vitro* studies using the frog sciatic nerve dosed over the concentration range of 0.01–1.0% butyraldehyde.⁽¹⁵⁾

V. HUMAN USE AND EXPERIENCE

There is contradictory evidence regarding the impact of skin exposure to humans. This material was reported to be mildly irritating in humans when applied to the skin.⁽¹⁵⁾ When tested at 1% in petrolatum, there was no irritation in humans after a 48-hr closed patch test (no volume given). In another report it was indicated that liquid butyraldehyde can cause skin and eye burns and that high vapor concentrations can cause irritation of the eyes, nose and throat with narcosis or anesthesia.⁽⁹⁾

Tested at 1% in petrolatum, 1 of 25 humans had a nonspecific sensitization reaction.⁽¹⁶⁾ Aliphatic aldehydes may be dermal sensitizers.

In six cases of industrial corneal injury from butyraldehyde, recovery was prompt and complete.⁽⁵⁴⁾

In a controlled study to test the potential irritancy of butyraldehyde, 15 males were exposed by inhalation to 230 ppm of butyraldehyde for 30 min and experienced no irritation.^(15,55) The lowest airborne concentration that produced irritation in humans was 580 mg/m³ (197 ppm; exposure duration not specified).

An epidemiology study of workers at an acetyl production plant indicated an increase in tumors of the nasal passage, oral cavity and bronchial airways; however, tumors appeared after a

relatively short exposure period and there was multiple chemical exposures (no levels reported). In a group of 150 factory workers with more than 20 years of exposure, 9 cases of carcinoma were reported although there were multiple aldehydes (including butyraldehyde) and alcohols detected in air.^(15,16)

A company Workplace Exposure Guideline (MWPEG) for butyraldehyde was referenced at 5 ppm or 15 mg/m³ as a 8 hour TWA based on eye and respiratory irritation or 10 ppm (30 mg/m³) STEL citing adequate protection against possible eye and respiratory irritation.⁽⁵⁶⁾ Health effects assessments at one government worksite indicated no worker hazard due to butyraldehyde exposure⁽⁵⁷⁾ and a health effects assessment of several workplace sites indicated that exposure levels were below the company exposure guidelines.^(39,56)

VI. RATIONALE

Butyraldehyde has a low odor threshold and, therefore, good warning properties at concentrations of approximately 10 ppm or less. Acute LD₅₀ data indicate a low order of toxicity by oral, dermal and inhalation routes of exposure. In terms of lethality, it is less toxic than similar aliphatic aldehydes (i.e. acetaldehyde and propionaldehyde) in several different animal species.^(58,59) Eye irritation studies indicate moderate to severe corneal injury with iritis following instillation of butyraldehyde into the eyes of rabbits. Human exposures reported prompt and complete recovery following corneal injury due to butyraldehyde exposure. Dermal exposure using liquid material applied to uncovered rabbit skin for 4 hours produced minor irritation, however, if the time period is extended to 24 hours and the skin abraded, then covered, severe irritation is reported in rabbits. When applied to the skin of humans, it is reported to be mildly irritating. If applied in 1% petrolatum, it is reported to not be irritating to human skin.¹⁰ In a separate report, butyraldehyde was reported to cause burns to the skin and eyes of humans. Also, high vapor concentrations (197- 230 ppm) can cause irritation to the eyes, nose and throat of humans. Butyraldehyde is expected to be metabolized rapidly and therefore would not be expected to accumulate in humans.

Genotoxicity studies in four different *in vitro* assays reported negative results. Equivocal results were obtained when evaluated for sex-linked recessive lethality. One study using Chinese V79 cells induced dose-dependent increases in mutation frequency. Another *in vitro* study using trypan-blue exclusion revealed Butyraldehyde caused a dose dependent decrease in survival of rat and human hepatocytes.

Developmental toxicity was evaluated by giving mice a single 1.0 mg/mouse intraperitoneal injection. This resulted in transient spermatogenic abnormalities, i.e., motility and morphology. Drinking water studies in mice using various exposure scenarios indicated chromosomal and meiotic anomalies at all stages of spermatogenesis. In a subsequent 90-day NTP gavage study in rats (75-300 mg/kg bw) and mice (150-600 mg/kg bw), the effects on sperm were not confirmed.

Several subacute and subchronic studies were conducted. The critical endpoint that occurs at the lowest dose, 117 ppm, reported is irritation of the eyes, nose and throat.

In one sub-chronic inhalation study, 117 ppm produced ocular and upper respiratory tract irritation in rats and dogs with relatively minor histological changes in the nasal cavity of both species. In another subchronic inhalation study in rats, 50 ppm was a no-observable effect level (NOEL) when body weights, serum chemistries, kidney or liver weights, ophthalmic or neurological exams or histological evaluations were performed.

The low acute lethality potential and the lack of systemic effects in subchronic inhalation studies indicate the WEEL for butyraldehyde should be based on its ocular and upper respiratory tract irritation. In a controlled study of 15 human males, none experienced irritation following exposure to 230 ppm for 30 minutes. Another human study indicated irritation could occur at 197 ppm (exposure duration not specified). Based on a structure-activity study of sensory irritation of inhaled aldehydes the authors recommended an exposure limit of 10–100 ppm butyraldehyde to prevent sensory irritation.⁽⁶⁰⁾ These same authors reported that saturated aliphatic aldehydes with two or more carbons, such as butyraldehyde, produced a RD50 value (concentration which elicits a 50% decrease in respiratory rate) from 750 – 4200 ppm.

The available toxicological literature supports the current WEEL guide of 25 ppm (8-hr TWA). This WEEL is based on a NOEL and is considered adequate to prevent mucous membrane irritation.

VII. RECOMMENDED WEEL

8-hr time-weighted average (TWA): 25 ppm (75 mg/m³)

This WEEL value was originally established in 1991 and updated in 2004. No significant new literature was identified since the last revision (2004) that supports a change to the recommended WEEL value.

VIII. REFERENCES

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