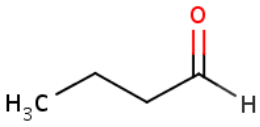
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

Butyraldehyde (2014)

I. IDENTIFICATION[1–15]

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: CH3CH2CH2 CHO



II. CHEMICAL AND PHYSICAL PROPERTIES[1–14]

Physical State: colorless liquid (at room temperature)
Molecular Weight: 72.1
Conversion Factors: 1mg/m^3 = 0.34 ppm
1 ppm = 2.95 mg/m^3 @ 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 × 10^5 to 1.21 × 10^5 ppm at 20 °C (68 °F)
Vapor Density (air =1): 2.5
Odor description: characteristic pungent, aldehyde odor
Odor threshold: low = 0.136 mg/m^3 (0.005 ppm); high = 26.55 mg/m^3 (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.[10] It is one of the major degradation products of polyvinylbutyral paint[11] and a moderate degradation product of epoxy, ethyl silicate, and latex paints.[12]

III. USES[16–20]

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 to1995 production volumes in the U.S. are listed as between 1.88 to 2.68 × 10^9 pounds.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Oral Toxicity[16–22]

LD_{50} = 2.5 – 5.9 g/kg

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[10,21,23–25]

Rabbit: 0.005 mL of a 15% solution produced moderate to severe corneal injury with iritis.

0.02 mL of neat material produced moderate to severe corneal injury with iritis and 0.005 mL (neat) produced trace to moderate corneal injury.

3. Skin Absorption

Rabbit: dermal LD_{50} 1.0 – 2.8 g/kg (24 hour occluded)[21]
Guinea pig: dermal LD_{50} >20 g/kg (no method provided)[10,17,20]

4. Skin Irritation

Rabbit: 0.01 mL of neat material on uncovered, clipped intact skin for 4 hr. produced minor irritation in two of five rabbits and no effect in the remaining three.[21]

Application to occluded intact or abraded skin (volume not provided) for 24 hr. produced severe irritation.[17] Moderate dermal irritation (methods not provided) was reported following application to guinea pigs.[10,16,17]

5. Skin Sensitization

Negative in a guinea pig sensitization test using 8 animals (4/sex).[25]

6. Inhalation Toxicity[16,17,20,26]

Rat (F-344): 50% decreased respiratory rate (RD_{50}), 5572 ppm

Species	Time	Route	LC_{50}
Mouse	2-hr	Inhalation	44,610 mg/m^3 (15,167 ppm)
Rat	4-hr	Inhalation	16,400 ppm
Rat	30-min	Inhalation	59,160 ppm anesthesia effect

7. Other

Species	Route	LD_{50}
Mouse	Intraperitoneal	1.14 g/kg[17]
Mouse	Subcutaneous	6.17 g/kg anesthesia, hemoglobinuria[27]
Rat	Intraperitoneal	0.8 g/kg[28]
Rat	Subcutaneous	10 g/kg anesthesia, hemoglobinuria[27]

B. Subacute Toxicity

Rats (numbers/strain not indicated) exposed by inhalation to butyraldehyde at a high dose of 2710 mg/m^3 (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/m^3 (320 ppm).[16]

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.[29–33]

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.[29–33]

Rats (ten female and ten male Sprague-Dawley) were exposed to 293, 930 and 2710 mg/m^3 (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.[34]

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.[16]

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). [16]

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, urinanalysis, 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 butyraldehydeexposed 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.[35–38]

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.[39]

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.[40,41]

D. Chronic Toxicity and Carcinogenicity

Evidence for the potential carcinogenicity of butyraldehyde is inconclusive.[8,9]

E. Reproductive/Developmental Toxicity

In one study a single intraperitoneal (i.p.) dose of 1 mg butyraldhyde/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.[9,16,42,43]

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.[44]

F. Genotoxicity/Mutagenicity

1. In vitro

Tests in *Salmonella typhimurium* TA98, TA100, TA1535 or TA 1537 either with or without microsomal enzymes were negative.[45–47] Equivocal results were obtained in Drosophila melanogaster when evaluated for sex-linked recessive lethality.[48–50] Butyraldehyde was not mutagenic in *Escherichia coli* when tested for reversion from streptomycin dependence.[51] It is not been shown to induced sister chromatid exchanges (SCE) in human lymphocytes treated *in vitro* for 24 and 48 hours[51,52] and was negative in inducing DNA repair synthesis (UDS) in human and rat hepatocyte primary cultures.[53]

2. In vitvo

In Chinese hamster V79 cells, butyraldehyde induced a dose-dependent increase in the frequency over controls of both 6-thioguanine and oubaine 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.[54,55]

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.[16]

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.[16]

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.[16] 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.[10]

Tested at 1% in petrolatum, 1 of 25 humans had a nonspecific sensitization reaction.[17] Aliphatic aldehydes may be dermal sensitizers.

In six cases of industrial corneal injury from butyraldehyde, recovery was prompt and complete.[56]

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.[16,57] The lowest airborne concentration that produced irritation in humans was 580 mg/m^3 (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.[16,17]

A company Workplace Exposure Guideline (MWPEG) for butyraldehyde was referenced at 5 ppm or 15 mg/m^3 as a 8 hour TWA based on eye and respiratory irritation or 10 ppm (30 mg/m^3) STEL citing adequate protection against possible eye and respiratory irritation.[58] Health effects assessments at one government worksite indicated no worker hazard due to butyraldehyde exposure[59] and a health effects assessment of several workplace sites indicated that exposure levels were below the company exposure guidelines.[41,58]

VI. RATIONALE

Butyraldehyde has a low odor threshold and, therefore, good warning properties at concentrations of approximately 10 ppm or less. Acute LD_{50} 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.[60,61] 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.[62] 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

An 8-hr time-weighted average (TWA) of 25 ppm (75 mg/m^3) is recommended for butyraldehyde.

VIII. REFERENCES

(1) National Library of Medicine. Toxicology Data Network http://toxnet.nlm.nih.gov/.

(2) Windholz, M.; Budavari, S.; Stroumtsos, L. Y.; Fertig, M. N. *The Merck Index 9th Edition*; Merck and Co. Inc: Rahway, NJ, 1976.

(3) Morrison, R. T.; Boyd, R. N. Organic Chemistry. In; Allyn and Bacon Inc: Boston, 1966; p. 599.

(4) Sax, N. I. Dangerous Properties of Industrial Chemicals. In; Van Nostrand Reinhold Co.: New York, 1979; p. 453.

(5) Aldehydes and Acetals. In *Patty's Industrial Hygiene and Toxicology*; Fasset, D. W.; Irish, D. D., Eds.; John Wiley and Sons: New York, 1963; pp. 1959–1989.

(6) Union Carbide Corporation. *Material Safety Data Sheet for Butyraldehyde*; Union Carbide Corporation: Danbury, CT, 1985.

(7) New Jersey Department of Health. *Right to Know Program, Hazardous Substance Fact Sheet. Butyraldehyde*; NJ Dept. Health: Trenton, NJ, 1996; pp. 1–6.

(8) NIOSH. *NIOSH Current Intelligence Bulletin No. 55: Carcinogenicity of Acetaldehyde and Malonaldehyde and Mutagenicity of Related Low-Molecular-Weight Aldehydes. ANON.*; 1991; p. 39.

(9) Eastman Kodak Company. *Toxicity and Health Hazard Data and Documents on N-Butyraldehyde with Cover Letter Dated 12/20/88. Doc #86-890000070*; Eastman Kodak Company: Rochester, NY, 1988.

(10) Henriks-Eckerman, M.; Engstrøm, B.; ÅNÄs, E. Thermal Degradation Products of Steel Protective Paints. *Am. Ind. Hyg. Assoc. J.* **1990**, *51*, 241–244.

(11) Peterson, J. E. Toxic Pyrolysis Products of Solvents, Paints, and Polymer Films. *Occup. Med. Phila. Pa* **1992**, *8*, 533–547.

(12) Matheson, D. Aldehydes and Ketals. In *Encyclopaedia of Occupational Health and Safety: Guides, indexes, directory*; International Labour Organization, 1998; Vol. 1, pp. 112–114.

(13) Ruth, J. H. Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review. *Am. Ind. Hyg. Assoc. J.* **1986**, *47*, A142–A151.

(14) United States Environmental Protection Agency. *OPPT Chemical Fact Sheets. Butyraldehyde Fact Sheet: Support Document (CAS No. 123–72–8). EPA 749-F-95-005a*; EPA/OTS Doc #88-920010574: Washington, DC, 1994.

(15) ChemID Plus. Butyraldehyde http://chem.sis.nlm.nih.gov/chemidplus/rn/123-72-8.

(16) Opdyke, D. L. N-Butyraldehyde. *Food Cosmet Toxicol* **1979**, *17*, 731–734.

(17) Smyth Jr, H. F.; Carpenter, C. P.; Weil, C. S.; Pozzani, U. C.; Striegel, J. A.; Nycum, J. S. Range-Finding Toxicity Data: List VII. *Am. Ind. Hyg. Assoc. J.* **1969**, *30*, 470–476.

(18) BASF Corp. *Material Safety Data Sheet for Butryaldehyde. Correspondence of Summary, Nov. 30, 1988. BASF Corp. 19.*; BASF Corporation: Danbury, CT, 1988.

(19) Union Carbide Corporation. *Chemical Hygiene Fellowship, Carnegie-Mellon University, Butyraldehyde: Ranging Finding Toxicity Studies. Report 40-73.*; Union Carbide Corporation: Danbury, CT, 1977.

(20) Chen, C.-Y.; Yeh, J.-T. Toxicity of Binary Mixtures of Reactive Toxicants. *Environ. Toxicol. Water Qual.* **1996**, *11*, 83–90.

(21) Spielmann, H.; Kalweit, S.; Liebsch, M.; Wirnsberger, T.; Gerner, I.; Bertram-Neis, E.; Krauser, K.; Kreiling, R.; Miltenburger, H. G.; Pape, W. Validation Study of Alternatives to the Draize Eye Irritation Test in Germany: Cytotoxicity Testing and HET-CAM Test with 136 Industrial Chemicals. *Toxicol. In Vitro* **1993**, *7*, 505–510.

(22) Bos, P. M. J.; Zwart, A.; Reuzel, P. G. J.; Bragt, P. C. Evaluation of the Sensory Irritation Test for the Assessment of Occupational Health Risk. *Crit. Rev. Toxicol.* **1992**, *21*, 423–450.

(23) United States Environmental Protection Agency. *Acute Toxicity, Primary Eye Irritation Studies in Rabbits, Dermal Sensitization Study in Guinea Pigs and Acute Inhalation Toxicity Study of C-243 in Rat W-Attachments and c-Letter. EPA/OTS Doc #86-890000095*; EPA/OTS: Washington, DC, 1989.

(24) Babiuk, C.; Steinhagen, W. H.; Barrow, C. S. Sensory Irritation Response to Inhaled Aldehydes after Formaldehyde Pretreatment. *Toxicol. Appl. Pharmacol.* **1985**, *79*, 143–149.

(25) Opdyke, D. L. J. Monographs on Fragrance Raw Materials. *Food Cosmet. Toxicol.* **1979**, *17*, 731–734.

(26) Skog, E. A Toxicologieal Investigation of Lower Aliphatic Aldehydes.: I. Toxicity of Formaldehyde, Acetaldehyde, Propionaldehyde and Butyraldehyde; as Well as of Acrolein and Crotonaldehyde. *Acta Pharmacol. Toxicol. (Copenh.)* **1950**, *6*, 299–318.

(27) Florin, I.; Rutberg, L.; Curvall, M.; Enzell, C. R. Screening of Tabacco Smoke Constituents for Mutagenicity Using the Ames' Test. *Toxicology* **1980**, *15*, 219–232.

(28) Sasaki, Y.; Endo, R. Mutagenicity of Aldehydes in Salmonella. *Mutat. Res. Mutagen. Relat. Subj.* **1978**, *54*, 251–252.

(29) United States Environmental Protection Agency. *Butyraldehyde: 9-Day Repeated Vapor Inhalation Toxicity, Vapor Inhalation By Dogs and Rats for 12 and 13 Weeks Respectively and a 12-Wk Vapor Inhalation Study in Rats, with Cover Letter Dated 02/06/89. EPA/OTS Doc #86-890000097*; U.S. EPA: Washington, DC, 1989.

(30) United States Environmental Protection Agency. *Initial Submission: Nine-Day Repeated Vapor Inhalation Toxicity Study of Butyraldehyde, with Cover Letter Dated 10/10/92.*

EPA/OTS Doc #88-920009661; U.S. EPA: Washington, DC, 1992.

(31) United States Environmental Protection Agency. *Initial Submission: Butyraldehyde Nine-Day Repeated Vapor Inhalation Toxicity Study, with Cover Letter Dated 08/20/92. EPA/OTS Doc #88-920006642.*; U.S. EPA: Washington, DC, 1992.

(32) BioDynamics Inc. *A Four Week Inhalation Toxicity Study of Butyraldehyde in the Rat, with Cover Letter Dated 12/28/88. EPA/OTS Doc. # 86-0000072. NTIS/OTIS0517382*; U.S. EPA: Washington, DC, 1989.

(33) United States Environmental Protection Agency. *Butryaldehyde Vapor Inhalation By Dogs and Rats for 14 and 13 Weeks Respectively and a 12 Week Vapor Inhalation Study in Rats with Attached Appendices, and Cover Letter Dated 02/22/88. EPA/OTS Doc #FYI-OTS-1088-0647D*; EPA/OTS: Washington, DC, 1978.

(34) Bushy Run Research Center. *Initial Submission: Vapor Inhalation in Dogs and Rats for 14 and 13 Weeks Respectively, with Cover Letter Dated 08/12/92. EPA/OTS Doc # 88-920007733*; U.S. EPA: Washington, DC, 1992.

(35) Haskell Laboratory. *Initial Submission: Vapor Inhalation by Dogs and Rats of Butyraldehyde for 14 and 13 Weeks, with Cover Letter Dated 10/15/92. EPA/OTS Doc. #88-920010226*; Environmental Protection Agency: Washington, DC, 1992.

(36) Haskell Laboratory. *Initial Submission: Vapor Inhalation by Dogs and Rats for 13 and 14 Weeks Respectively, with Cover Letter 09/01/92. EPA/OTS Doc. #88-920008339*; Environmental Protection Agency: Washington, DC, 1992.

(37) Carnegie-Mellon Institute. *Initial Submission: Vapor Inhalation by Dogs and Rats for 13 and 14 Weeks Respectively, with Cover Letter 08/10/92. EPA/OTS Doc. #88-920010404*; Environmental Protection Agency: Washington, DC, 1992.

(38) Union Carbide Corporation. *Chemical Hygiene Fellowship, Carnegie-Mellon University, Butyraldehyde: Twelve-Week Vapor Inhalation Toxicity Study in Rats. Report 43-61*; Union Carbide Corporation: Danbury, CT, 1978.

(39) Stefanski, S. A. Review of Butyraldehyde by Gavage in Fisher Rats and B6C3F1 Mice 90-Day Study. In *U.S. Dept. of Health and Human Services: Pathology Working Group (PWG)*; National Toxicology Program: Research Triangle Park, NC, 1987.

(40) United States Environmental Protection Agency. *Health and Safety Information for Butyraldehyde, with Cover Letter Dated 02/13/89 (Sanitized). EPA/OTS Doc. #86-890000162S.*; U.S. EPA: Washington, DC, 1989.

(41) McLaughlin, R. S.; Carpenter, C.; Smyth, H. F. Chemical Burns of the Human Cornea; Chemical Burns of the Rabbit Cornea. *Am. J. Ophthalmol.* **1946**, *29*, 1355–1372.

(42) Auerbach, C.; Moutschen-Dahmen, M.; Moutschen, J. Genetic and Cytogenetical Effects of Formaldehyde and Related Compounds. *Mutat. Res. Genet. Toxicol.* **1977**, *39*, 317–361.

(43) United States Environmental Protection Agency. *Initial Submission: Nine-Day Repeated Vapor Inhalation Toxicity Study of Butyraldehyde Vapor in Rats, Mice, Guinea Pigs, Rabbits and Dogs, with Cover Letter Dated 09/01/92. EPA/OTS Doc #88-920008376*; EPA/OTS: Washington, DC, 1992.

(44) United States Environmental Protection Agency. *Initial Submission: Nine-Day Repeated Vapor Inhalation Toxicity Study of Butyraldehyde Vapor in Rats, Mice, Guinea Pigs, Rabbits and Dogs, with Cover Letter Dated 10/15/92. EPA/OTS Doc #88-920010574*; U.S. EPA: Washington, DC, 1992.

(45) Mortelmans, K.; Haworth, S.; Lawlor, T.; Speck, W.; Tainer, B.; Zeiger, E. Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. *Environ. Mutagen.* **1986**, *8 Suppl 7*, 1–119.

(46) Mason, J. M.; Valencia, R.; Zimmering, S. Chemical Mutagenesis Testing in Drosophila: VIII. Reexamination of Equivocai Results. *Environ. Mol. Mutagen.* **1992**, *19*, 227–234.

(47) Valencia, R.; Mason, J. M.; Woodruff, R. C.; Zimmering, S. Chemical Mutagenesis Testing in Drosophila. III. Results of 48 Coded Compounds Tested for the National Toxicology Program. *Environ. Mutagen.* **1985**, *7*, 325–348.

(48) Dillon, D. M.; McGregor, D. B.; Combes, R. D.; Zeiger, E. Detection of Mutagenicity in Salmonella of Some Aldehydes and Peroxides. *Environ.Mol.Mutagen* **1992**, *19*, 15.

(49) Szybalski, W. Special Microbiological Systems. II. Observations on Chemical Mutagenesis in MICROORGANISMS*. *Ann. N. Y. Acad. Sci.* **1958**, *76*, 475–489.

(50) Obe, G.; Beek, B. Mutagenic Activity of Aldehydes. *Drug Alcohol Depend.* **1979**, *4*, 91–94.

(51) Tucker, J. D.; Auletta, A.; Cimino, M. C.; Dearfield, K. L.; Jacobson-Kram, D.; Tice, R. R.; Carrano, A. V. Sister-Chromatid Exchange: Second Report of the Gene-Tox Program. *Mutat. Res. Genet. Toxicol.* **1993**, *297*, 101–180.

(52) Martelli, A. Primary Human and Rat Hepatocytes in Genotoxicity Assessment. *Vivo Athens Greece* **1997**, *11*, 189–193.

(53) Brambilla, G.; Cajelli, E.; Canonero, R.; Martelli, A.; Marinari, U. M. Mutagenicity in V79 Chinese Hamster Cells of N-Alkanals Produced by Lipid Peroxidation. *Mutagenesis* **1989**, *4*, 277–279.

(54) Martelli, A.; Canonero, R.; Cavanna, M.; Ceradelli, M.; Marinari, U. M. Cytotoxic and Genotoxic Effects of Five N-Alkanals in Primary Cultures of Rat and Human Hepatocytes. *Mutat. Res.* **1994**, *323*, 121–126.

(55) Moutschen-Dahmen, J.; Moutschen-Dahmen, M.; Degraeve, N.; Houbrechts, N.; Colizzi, A. Proceedings: Genetical Hazards of Aldehydes from Mouse Experiments. *Mutat. Res.* **1975**, *29*, 205.

(56) Sim, V. M.; Pattle, R. E. Effect of Possible Smog Irritants on Human Subjects. *J. Am. Med. Assoc.* **1957**, *165*, 1908–1913.

(57) United States Environmental Protection Agency. *Health Effects Assessment for Butyraldehyde at the Decatur Plant (Final Report) with Attachments, and Cover Letter Dated 12/28/89. EPA/OTS Doc. #86-90000051*; U.S. EPA: Washington, DC, 1989.

(58) Ahrenholz, S. H. *Health-Hazard Evaluation Report HETA 87-266-1860, US Department of the Treasury, Bureau of Engraving and Printing, Washington, DC*; National Institute for Occupational Safety and Health: Cincinnati, OH, 1988.

(59) United States Environmental Protection Agency. *Health Effects Assessment for Butyraldehyde at the Trenton, Decatur and Nitro Plants (Final Report) with Attachments, and Cover Letter Dated 12/28/89. EPA/OTS Doc. #86-90000044*; U.S. EPA: Washington, DC, 1989.

(60) Salem, H.; Cullumbine, H. Inhalation Toxicities of Some Aldehydes. *Toxicol. Appl. Pharmacol.* **1960**, *2*, 183–187.

(61) Henson, E. V. The Toxicology of Some Aliphatic Aldehydes. *J. Occup. Environ. Med.* **1959**, *1*, 457–462.

(62) Steinhagen, W. H.; Barrow, C. S. Sensory Irritation Structure-Activity Study of Inhaled Aldehydes in B6C3F1 and Swiss-Webster Mice. *Toxicol. Appl. Pharmacol.* **1984**, *72*, 495–503.