ISOBUTYRALDEHYDE

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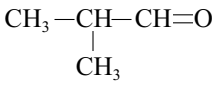
I. IDENTIFICATION

Chemical Name: Isobutyraldehyde
Synonyms: Isobutanal; 2-methylpropanal; isobutyric aldehyde; isobutyl aldehyde; 2-methylpropionaldehyde; 2-methyl-1-propanal; valine aldehyde
CAS Number: 78–84–2
Molecular Formula: C_4H_8O
Structural Formula:



II. PHYSICAL AND CHEMICAL PROPERTIES[1-3]

Physical State and Appearance: Colorless liquid
Odor Description: Sweet, ester, pleasant to unpleasant, pungent
Odor Threshold: 1–44 ppb
Molecular Weight: 72.1
Conversion Factors: 1 ppm = 2.9 mg/m^3;
1 mg/m^3 = 0.34 ppm
Melting Point: -65.9°C (-86.62°F) at 760 mm Hg
Boiling Point: 64°C (147.2°F) at 760 mm Hg
Vapor Pressure: 170 mm Hg at 20°C (68°F)
Saturated Vapor Concentration: 224,000 ppm at 20°C (68°F)
Vapor Density: 2.48
Specific Gravity (Water = 1): 0.7938
Flammable Limits: 10.6%
Flash Point (open cup): <-7 ºC (< 20°F)
Solubility: Isobutyraldehyde is miscible with ethanol, ether, carbon disulfide, acetone, benzene, toluene, and chloroform. Its solubility in water is approximately 7.5% by weight.
Stability and Incompatibilities: Oxidizes slowly upon exposure to air, forming isobutyric acid. Oxidation can also cause formation of hazardous peroxides or peracids. May react vigorously with reducing materials; contamination with basic materials, mineral acids, and iron oxides can result in a rapid exothermic reaction.[4]

III. USES[3]

Isobutyraldehyde's primary use is as a reactive intermediate. Most isobutyraldehyde is consumed captively for manufacture of derivatives such as isobutanol, neopentyl glycol, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate, and its diester, isobutylisobutyrate, and other smaller derivatives. Isobutyraldehyde is also utilized as a pesticide intermediate. Other uses include the organic synthesis of gasoline additives, perfumes, plasticizers, and specialty chemicals, including amino acids and flavoring agents. Production and conversion to other chemicals necessarily takes place in closed systems because of the volatile and flammable nature of this chemical. Isobutyraldehyde is transported between site locations by bulk carrier; these practices minimize workplace exposure. Isobutyraldehyde, as a reactive intermediate, is not directly contained in products reaching the consumer.

IV. ANIMAL TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Rats: LD_{50}, 3730 mg/kg (females)[5]
LD_{50}, 1600–3200 mg/kg[6]

2. *Eye Toxicity*

Rabbits: A volume of 0.02 ml isobutyraldehyde instilled into the conjuctival sac resulted in severe corneal damage. Instillation of a lesser volume (0.005 ml) caused moderate corneal injury.[5]

3. *Absorption*

Rabbits: LD_{50} ~ 7.1 ml/kg (5.6 g/kg) (males)[5]
Guinea Pig: LD_{50} > 20 g/kg (4-hr test)[6]

4. *Skin Irritation*

Rabbits: Application of 0.01 ml undiluted isobutyraldehyde to the uncovered clipped

skin of rabbits produced no reaction or irritation, possibly because of rapid evaporation. Occluded contact with large quantities (up to 10 ml/kg or 7940 mg/kg) of isobutyraldehyde for 24 hours resulted in edema, redness, and necrosis.[5]

Mice: Isobutyraldehyde was applied directly to shaved and abraded ears for five consecutive days. Doses applied ranged from 3–30% in a 4:1 solution of acetone and olive oil. No irritation was observed.[7]

5. Skin Sensitization

Mice: The potential for isobutyraldehyde to elicit sensitization was tested in the Murine Local Lymph Node Assay. Isobutyraldehyde was applied directly to shaved and abraded ears of mice for five consecutive days with and without adjuvant. Doses applied ranged from 3–30% in a 4:1 solution of acetone and olive oil for sensitization, and 30% for challenge. There was no indication of irritation or hypersensitivity.[7]

6. Inhalation Toxicity

Substantially saturated vapor generated at room temperature killed 4/6 rats exposed for 30 minutes, and 0/6 rats exposed for 15 minutes. When groups of rats were exposed to isobutyraldehyde vapor for four hours; 16,000 ppm killed 6/6 rats while 8,000 ppm killed 1/6.[5]

The vapor concentration of isobutyraldehyde capable of causing a 50% reduction in respiratory rate (RD_{50}) during a 10-min, head-only exposure, was 3016 ppm (95% confidence interval 2568–3610) in male B6C3F1 mice, and 4167 ppm (95% confidence interval 3258–5671) in male Swiss-Webster mice.[8]

7. Intraperitoneal Toxicity

Rat: LD_{50} = 1600–3200 mg/kg[6]

B. Subacute Toxicity

Isobutyraldehyde was administered by inhalation to groups of four male and female Alderley Park SPF rats 6 hr/day for 12 consecutive days at 1000 ppm. There were no deaths and no evidence of systemic toxicity during exposure. Animals exhibited symptoms of slight nasal irritation. Upon necropsy, organs appeared normal. Microscopic examination of tissues revealed no nasal pathology.[9]

C. Subchronic Toxicity

Groups of 10 male and female F-344 rats and 10 male and female B6C3F1 mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, 2000, 4000, or 8000 ppm. Animals were exposed for 6 hr/day, 5 days/week for 13 weeks. All animals exposed to 8000 ppm died before the end of the study. Mortality among animals exposed to 4000 ppm was 90% and 100% in male and female mice, and 30% and 60% in male and female rats, respectively. Severe degenerative and inflammatory changes in the nasal and olfactory epithelium were observed in mice and rats exposed to 4000 and 8000 ppm. Minimal to mild degeneration of the olfactory epithelium was observed in rats and mice exposed to 2000 ppm. Epithelial hyperplasia and suppurative inflammation were noted in some mice in the 1000-ppm group. There were no treatment-related lesions in the respiratory tract of rats exposed to 1000 and 500 ppm, and mice exposed to 500 ppm. The no observable effect level (NOEL) was 1000 ppm for rats and 500 ppm for mice.[10]

D. Chronic Toxicity/Carcinogenicity

Rats: Groups of 50 male and female F-344 rats were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm. Animals were exposed for 6 hr/day, 5 days/week for 2 years. There was no significant difference in survival rates between exposed or control groups; there were no clinical findings that could be attributed to isobutyraldehyde exposure. The only exposure-related effects observed were non-neoplastic nasal lesions.

Exposure-related lesions of the nose included olfactory epithelial degeneration, suppurative inflammation, and squamous metaplasia of the respiratory epithelium in rats exposed to 2000 ppm. Mild to minimal squamous metaplasia was noted in male and female rats exposed to 1000 ppm, and female rats exposed to 500 ppm.

No increase in incidence of neoplasms was observed in either sex that could be attributed to treatment. Three nasal tumors were observed in three exposed rats (one male at 1000 and 2000 ppm, and one female at 500 ppm). Because these neoplasms were of different histiogenic origin and there was no dose-related response, they were not considered related to isobutyraldehyde exposure.[10]

Mice: Groups of 50 male and female B6C3F1 mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm. Animals were exposed for 6 hr/day, 5 days/week for 2 years. The survival rate of males exposed to 2000 ppm was significantly reduced. There were no differences in survival rates among exposed females. Mean body weights of female mice exposed to 1000 and 2000 ppm were lower than

those of controls during the second year of the study. There were no other clinical findings that could be attributed to isobutyraldehyde exposure. The only exposure-related effects observed were non-neoplastic nasal lesions.

Exposure-related lesions were limited to degeneration of the olfactory epithelium in mice exposed to 2000 and 1000 ppm; two mice in each group displayed necrosis of the olfactory epithelium. There were no nasal lesions in mice exposed to 500 ppm. There was no increase in tumor incidence in mice at any concentration level.[10]

Based on body weight changes, survival, and incidence and severity of exposure-related lesions observed at higher doses, 2000-ppm isobutyraldehyde was considered to be the maximally tolerated dose for rats and mice in these 2-year NTP studies. Exposure concentrations were considered sufficiently high for determining the lack of carcinogenic potential of isobutyraldehyde.[10]

E. Reproductive/Developmental Toxicity

1. Inhalation Study (Mouse and Rat)

Groups of 10 male and female F-344 rats and 10 male and female B6C3F1 mice were exposed to isobutyraldehyde. Rats were exposed at concentrations of 0, 500, 1000, 2000, or 4000 ppm; mice were exposed to 0, 500, 1000, or 2000 ppm. Animals were exposed for 6 hr/day, 5 days/week for 13 weeks. Decreased body weight was noted in rats exposed to 4000 ppm. In male rats, decreased absolute but not relative weight of the right cauda epididymis and right epididymis was observed in rats exposed to 4000 ppm. There were no changes in sperm motility, density, or morphology. No weight change of reproductive organs or effects on sperm motility, density, or morphology were noted in male mice exposed to concentrations up to 2000 ppm. There was no effect on vaginal cytology in females at any concentration tested.[11]

2. Inhalation Study (Mouse and Rat)

Groups of male and female F-344 rats and male and female B6C3F1 mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm. Animals were exposed for 6 hr/day, 5 days/week for 2 years. The survival rate of male mice exposed to 2000 ppm was significantly reduced. There was no effect on survival among female mice, or male and female rats. Mean body weights of female mice exposed to 1000 and 2000 ppm were lower than those of controls during the second year of the study. There were no other clinical findings that could be attributed to isobutyraldehyde exposure. At the end of the 2-year study, reproductive organs were normal upon gross and histopathological examination.[10]

3. Inhalation Developmental Study (Rat)

Groups of mated female Wistar rats were exposed to 0, 1000, 2500, or 4000-ppm isobutyraldehyde for 6 hr/day on post-coital day 6 through post-coital day 15. Clinical examinations of animals were performed before, during and after the exposure interval. Animals were sacrificed on day 20, after a 5-day post-exposure observation period. Isobutyraldehyde treatment resulted in a dose-related increase in maternal toxicity, as evidenced by a significant decrease in body weight gain in dams exposed to 4000 and 2500 ppm, but not at 1000 ppm. Exposure of dams to isobutyraldehyde vapor during organogenesis had no effect on gestational or litter parameters and did not induce embryofetal toxicity. There was no increase in fetal malformations at any exposure level, up to the highest concentration tested, 4000 ppm.[12]

F. Genotoxicity/Mutagenicity

1. In Vitro Studies

Isobutryaldehyde was negative in seven strains of *Salmonella typhimurium* at concentrations up to 10,000 ug/plate, in the presence and absence of rat, mouse, or hamster S-9 metabolic activation.[13–16] One group, using a modification of the Ames Test, reported that isobutyraldehyde induced a positive response in the absence of metabolic activation; however the doses used, plate counts, and the strains which tested positive were not reported.[17]

2. In Vivo Studies

Isobutyraldehyde was tested as a coded chemical in *Drosophila melanogaster* by adult feeding and by injection. Adult Canton-S wild-type males were fed 50,000-ppm isobutyraldehyde in water, or were injected with an aqueous solution containing 80,000-ppm isobutyraldehyde. Mortality was approximately 30% of treated flies. Following treatment, males were mated to Basc virgin females; three broods were analyzed. There was no increase in sex-linked recessive lethal mutations in meiotic and post-meiotic male germ cells.[18]

G. Metabolism/Pharmacokinetics

Isobutyraldehyde readily oxidizes to isobutyric acid via aldehyde dehydrogenase (ALDH).[6] Isobutyraldehyde has also been shown to undergo *in vitro* oxidative deformylation, catalyzed by rabbit liver cytochrome P-450, to yield propylene and formic acid.[19]

V. HUMAN USE AND EXPERIENCE

No irritation was experienced by 15 males exposed to 210 ppm (620 mg/m^3) of isobutyraldehyde for 30 minutes; however, nausea was noted by some subjects and one subject vomited.[20]

Isobutyraldehyde is an FDA-approved food-flavoring agent and is a naturally occurring food and beverage constituent. It is found in apple and currant aromas, and in the essential oils from tobacco and tea leaves; isobutyraldehyde is also found in essential oils of *Pinus jeffreyi murr, Citrus aurantium,* and *Datura stramonium*.[21] Other sources of isobutyraldehyde in the environment include combustion of gasoline, diesel fuel, and wood. Degradation of animal wastes and vegetation also release isobutyraldehyde.[22]

The potential for occupational exposure is most likely to occur at sites where isobutyraldehyde is produced or used as a chemical intermediate. Industrial hygiene sampling was conducted at one production site between 1990 and 1995 in order to establish an exposure baseline for isobutyraldehyde. A total of 27 samples were collected; the bulk of the results were less than 0.010 ppm. Two samples yielded measurable 8-hr time-weighted average (TWA) concentrations of 12 and 18 ppm. Similar data have also been collected at a European production facility. A total of 217 personal monitoring samples were collected between 1979 and 1996. Readings ranged between 0 and 7 ppm, the average for all samples was 0.2 ppm.[23]

VI. RATIONALE

As with other aldehydes, isobutyraldehyde is an irritant to the eyes, skin, and upper respiratory tract. Toxicological data indicate that adverse acute and chronic effects occur only at fairly high dosages, and overall toxicity is moderate. Isobutyraldehyde was not carcinogenic at concentrations up to 2000 ppm in rats and mice; there were no embryotoxicity or developmental effects observed in offspring of rats exposed up to 4000 ppm.

Isobutyraldehyde is anticipated to be metabolized and is not expected to accumulate in humans. The low acute lethality potential and lack of systemic effects suggest that the OEL can be based upon ocular and upper respiratory tract irritancy. Using the correlation between RD_{50} measurements and exposure limits,[24,25] a level between 25 and 75 ppm would protect against upper respiratory tract irritation; this is similar to the TWA range recommended by Steinhagen and Barrow.[8] However, in a 2-year study, effects on the nasal epithelium were noted in both sexes of rats and mice exposed to 1000 ppm; minimal changes were noted in some female rats exposed to 500 ppm.[10] Therefore, a OEL Guide of 25 ppm is expected to provide an adequate margin of safety to prevent irritation and related effects as well as to minimize or prevent nausea.

VII. RECOMMENDED OEL

8-hr TWA: 25 ppm

VIII. REFERENCES

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