PROPIONALDEHYDE

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I. IDENTIFICATION

Chemical Name: Propionaldehyde
Synonyms: 1-Propanal; methylacetaldehyde; propylaldehyde
CAS Number: 123–38–6
Molecular Formula: C_3H_6O
Structural Formula: CH_3-CH_2-CH=O

II. PHYSICAL AND CHEMICAL PROPERTIES[1-5]

Physical State and Appearance: Colorless liquid
Odor Description: Suffocating, pungent, irritating, unpleasant
Odor Thresholds: Absolute perception limit: 0.009 ppm;
50% recognition limit: 0.040 ppm;
100% recognition limit: 0.080 ppm
Molecular Weight: 58.1
Conversion Factors: 1 ppm = 2.38 mg/m^3;
1 mg/m^3 = 0.42 ppm
Melting Point: -81°C (-113.8°F) at 760 mm Hg
Boiling Point: 49°C (120.2°F) at 760 mm Hg
Vapor Pressure: 235 mm Hg at 20°C (68°F);
317 mm Hg at 25°C (77°F);
687 mm Hg at 45°C (113°F)
Saturated Vapor Concentration: 309,000 at 20°C (68°F); 409,000 at 25°C (77°F)
Flash Point (open cup): < -7 ºC (< 20°F)
Flammable Range: 2.9–17%
Specific Gravity (Water = 1): 0.807
Vapor Density: 2.0
Solubility: Propionaldehyde is miscible with alcohol, chloroform, and ether. Its solubility in water is approximately 20% by weight.
Reactivity and Incompatibilities: Reacts vigorously with oxidizers; polymerization may occur in the presence of acids or caustics. Contamination with basic materials, mineral acids, or iron oxides can result in a rapid exothermic reaction. Oxidation can cause formation of hazardous peroxides or peracids.[6]

III. USES[3]

Propionaldehyde is used primarily as a reactive intermediate in the manufacture of propanol, propionic acid, rubber chemicals, polyvinyls and other plastics, fragrances, and fungicides. Production and conversion to other chemicals necessarily take place in closed systems because of the volatile and flammable nature of this chemical. Propionaldehyde is transported between site locations by pipeline or bulk carrier; these practices minimize workplace exposure. Propionaldehyde, 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}: 1410 mg/kg (males)[7,8]
LD_{50}: 1690 mg/kg (females)[9]

2. Eye Toxicity

Rabbits: A volume of 0.1 ml propionaldehyde instilled into the corneal sac resulted in minor transient corneal injury and iritis. Moderate to severe conjuctival irritation was observed within 1 to 48 hours. At 24 to 72 hours, hemorrhages were apparent on the nictitating membranes. Within 7 days, only minor conjuctival redness remained; all eyes were normal at 10 and 14 days after exposure. Instillation of a lesser volume (0.01 ml) had similar results but more rapid recovery; all eyes were normal within 7 days after exposure.[9]

Rabbits: The instillation of 20 mg resulted in moderate irritation at 24 hours.[10]

3. *Skin Absorption*

Rabbits: LD_{50}: 2460 mg/kg (females); 2000 mg/kg killed 1/3 males[9]
LD_{50}: 5.0 ml/kg (4035 mg/kg) (males)[7,8]

4. *Skin Irritation*

Rabbits: Application of 0.5 ml to covered rabbit skin for a 4-hr contact period produced minor to moderate redness and moderate edema. Superficial necrosis and desquamation developed within 7–14 days. At 14 days, there was no edema or redness; fissuring, scabs, or alopecia were apparent on a few animals.[9]

5. *Skin Sensitization*

Guinea pig: Propionaldehyde was applied to the skin using a "drop-on" technique at a concentration of 0.1 M in an acetone:dioxane: guinea pig fat (1:1:1) vehicle. Phenylhydrazine was employed as the positive control. Although the exact details of the protocol used are not available, it is likely that the test material was applied repeatedly over 10 days during a 2-week period and then again once in the fourth and fifth weeks. The later observations would include not only an irritation component, but also a sensitization component. Propionaldehyde was irritating to the skin but was considered negative for sensitization under the conditions of the test.[11]

6. *Inhalation Toxicity*

Rats: LC_{50}: 62 mg/L (62,000 mg/m^3; 26040 ppm)[12]

Mice: LC_{50}: 21800 mg/m^3 (9156 ppm) (2-hr exposure)[13]

Rats exposed to 16000 ppm died within 2.25 hours and 8000 ppm killed 5/6 rats within 4 hours. There was no mortality among rats exposed to 4000 ppm for 4 hours. Substantially saturated vapor dynamically generated at room temperature (approximately 300,000 ppm) killed 6/6 rats in 10 minutes, 2/6 in 5 minutes, and 0/5 in 2 minutes.[8]

Groups of 50 mice, 20 guinea pigs, and 5 rabbits were exposed to propionaldehyde in aerosol and vapor form for periods of up to 10 hours or until death occurred; doses were expressed as milligram-minutes per cubic meter. Mean fatal doses were 790,000 and 740,000 mg-min/m^3 for mice and rabbits, respectively. All guinea pigs survived exposure; the exposure concentration was not reported. All animals developed pulmonary edema as evidenced by necropsy findings.[14]

The vapor concentration of propionaldehyde capable of causing a 50% reduction in respiratory rate (RD_{50}) during a 10-min, head-only exposure was 2070 ppm (95% confidence interval 1803 to 2402) in B6C3F1 male mice, and 2052 ppm (95% confidence interval 1625–3040) in male Swiss-Webster mice.[15] The RD_{50} in Fischer-344 rats was 6789 ppm.[16]

7. *Intraperitoneal Toxicity*

Mice: LD_{50}: 960 mg/kg[17]

B. Subacute Toxicity

Propionaldehyde was administered by inhalation to male and female Alderley Park SPF rats 6 hr/day for 6 consecutive days at 1300 ppm. There were no deaths; animals did not gain weight during the exposure interval. Upon necropsy, organs appeared normal. Microscopic examination of selected tissues (lung, liver, kidneys, spleen, and adrenals) revealed cell vacuolization of the liver.[18]

Groups of 4 male and female Alderley Park SPF rats were exposed to 90 ppm for 6 hr/day, 5 days/week, for 4 weeks (20 exposures). There were no deaths and animals did not exhibit signs of toxicity or irritation during the exposure interval. Urinalysis and hematology tests were normal. Upon necropsy, organs appeared normal. Microscopic examination of tissues revealed no pathology. However, nasal tissues were not examined.[18]

C. Subchronic Toxicity

Groups of male and female CD rats were exposed to propionaldehyde vapor at concentrations of 0, 150, 750, or 1500 ppm for 6 hr/day, 7 days/week. Males were exposed for 52 days; females were exposed for 48 days and then held for a 6-day recovery interval before sacrifice. Animals did not display overt signs of toxicity at any time during the study. Body weight gains and food consumption, however, were decreased in females in the 750- and 1500-ppm groups during the first week of exposure. Microscopic examination revealed treatment-related effects on the nasal epithelium in the anterior two sections of the nasal cavity in both sexes in all propionaldehyde-exposed groups. Vacuolization of the nasal epithelium was primarily evident in the 150-ppm and 750-ppm groups; atrophy was observed in the 750-ppm and 1500-ppm groups. The injury appeared to be diminished in females, possibly as a result of the 6-day recovery interval.[19]

In an unverifiable report, rats exposed to 4 mg/m^3 (~1.7 ppm) of propionaldehyde for 24 hr/day for 75 days exhibited CNS effects and reductions in red blood cell count, hemoglobin concentration and cholinesterase of the peripheral blood.[20] No additional details are available. Various limitations in the study protocol and report do not allow for a determination of the validity of the findings.

D. Chronic Toxicity/Carcinogenicity

No data available.

E. Reproductive/Developmental Toxicity

1. One-Generation Inhalation Study (Rat)

Male and female rats were exposed to propionaldehyde by inhalation for 6 hr/day, 7 days/week, at concentrations of 0, 150, 750, or 1500 ppm. Males received 52 consecutive daily exposures; females were exposed through gestation day 20, for a maximum of 48 days. Females were allowed to litter. Pup body weight, viability, and survival were monitored from birth until post-natal day 4, when both females and their offspring were sacrificed and subjected to necropsy. No significant effects of exposure were noted on any reproductive parameter assessed. Mating index and fertility index for males and females, and the gestation index for females, were not affected. Litter size and viability were similar among all groups; pup body weights were not affected by exposure, although the body weight gain of pups from the 1500-ppm group was slightly depressed.[19]

2. Intraamniotic Injection Developmental Study (Rat)

Timed-pregnant female Sprague-Dawley rats were laparotomized under anesthesia on gestation day 13. Embryos in one uterine horn received an intraamniotic injection of propionaldehyde at doses of 10, 100, or 1000 ug/embryo. Females were killed on gestation day 20. Uterine horns were removed and the number of dead or resorbed fetuses was determined. Live fetuses were examined for external malformations. Propionaldehyde treatment resulted in a dose-dependent increase in embryo mortality. The increase in embryolethality was significant at the highest dose of 1000 ug/embryo when compared to saline-injected controls. There was no increase in fetal malformations up to the highest concentration tested, 1000 ug/embryo.[21]

F. Genotoxicity/Mutagenicity

1. In Vitro Studies

Propionaldehyde 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.[22-25] Propionaldehyde induced a dose-dependent increase in mutation frequency in Chinese hamster V79 cells in the absence of metabolic activation.[26] Chinese hamster ovary (CHO) cells exposed to propionaldehyde displayed a weak increase in the incidence of lagging chromosomes when compared to untreated controls. There was, however, no difference between control and treated cell cultures in the frequency of chromatin bridges or lagging fragments.[27]

2. In Vivo Studies

Propionaldehyde was administered to groups of male and female Swiss-Webster mice as a single intraperitoneal injection at doses of 240, 480, or 768 mg/kg (25%, 50%, or 80% of the LD_{50}, respectively). Animals were sacrificed at 12, 24, and 48 hours after treatment; bone marrow was collected and a minimum of 1000 polychromatic erythrocytes were examined for the presence of micronuclei. Although the high dose males had a higher incidence of micronuclei than concurrent vehicle controls, the overall incidences of micronuclei and the distribution of micronuclei were within normal ranges when compared to historical controls. Propionaldehyde was not considered to be an inducer of micronuclei under the conditions of this *in vivo* test.[28]

G. Metabolism/Pharmacokinetics

Propionaldehyde is a reactive molecule and readily oxidizes to propionic acid via aldehyde dehydrogenase (ALDH). Propionaldehyde has been demonstrated to be a substrate for ALDH. Propionaldehyde dehydrogenase activity has been identified in tissue preparations from mice,[29] rats,[30,31] and humans.[32]

Retention of propionaldehyde in the respiratory tract of anesthetized dogs was 75–80% of the inhaled dose at concentrations between 250 and 1000 mg/m^3 (100 and 400 ppm). Similar retentions were also measured in dogs at tidal volumes ranging from approximately 100–200 ml.[33] Propionaldehyde acted as a vasopressor agent when injected intravenously into anesthetized dogs[34] and rats.[35]

V. HUMAN USE AND EXPERIENCE

Mild irritation of mucosal surfaces was reported in 12 males following exposures to 324 mg/m^3 (134 ppm) propionaldehyde for 30 minutes; there was only an occasional comment about odor.[36]

Propionaldehyde is a food flavoring agent and is a naturally occurring coffee and apple aroma constituent. Propionaldehyde is a product of wood, gasoline, diesel, and polyethylene combustion.

According to the National Ambient Volatile Organic Compounds (VOCs) Database, the median urban concentration of propionaldehyde was 17.2 ppb for 22 samples. Concentrations in Jones State Forest, TX ranged from 1.8 to 39.9 ppb, with an average of 18.8 ppb for 5 samples. The median remote atmospheric concentration of propionaldehyde was 0.993 ppb for three samples.[3] Office workers for the USEPA at 65 locations in three headquarter buildings were exposed to average concentrations of 0.91 ug/m^3 (0.373 ppb) propionaldehyde.[37]

Minimal occupational exposure is likely to occur at sites where propionaldehyde is produced or used as a chemical intermediate. In the 17-year period between 1975 and 1992, a total of 73 personnel samples had been taken within the "Oxo" production unit of Union Carbide. Of these, 62 (>85%) were below the detection limit of 0.01 ppm. The maximum time-weighted average (TWA) measured over this interval was 26 ppm and the geometric mean for all 73 TWA determinations was 0.02 ppm. In the same timeframe, 16 TWA determinations were made within the In-Plant Distribution Department. Of these, 8 (50%) were below the detection limit of 0.01 ppm. In one or two instances, excursions in the range of 100 ppm were determined, but the geometric mean for all 16 samples was still in the range of 1 ppm.[38]

At one facility, propionaldehyde was charged from drums to a reactor in a chemical synthesis batch process that was run intermittently. Workers wore full-face supplied-air respirators and protective clothing during the transfer operations. Air sampling was conducted during the 30-min task; the average concentration on one occasion was 8.4 ppm, while 51 ppm was obtained on another occasion. After one operation was completed, air sampling revealed that propionaldehyde levels were less than 0.2 ppm; however, a lingering offensive odor was noted throughout the area.[39]

VI. RATIONALE

As with other aldehydes, propionaldehyde is a severe eye irritant and is irritating to the 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.

Propionaldehyde 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 on ocular and upper respiratory tract irritancy. Using the correlation between RD_{50} measurements and exposure limits,[40] an OEL between 15 and 50 ppm would be indicated. This range is within the TWA range recommended by Steinhagen and Barrow,[15] and less than the range rec-ommended by Alarie.[41] In a subchronic study, rhinitis, and atrophy and vacuolization of the olfactory epithe-lium were observed in rats exposed to 750 ppm. Mini-mal to mild vacuolization of the olfactory epithelium was noted in rats exposed to 150 ppm.[19] An OEL guide of 20 ppm is recommended to prevent irritation and possible minimal changes in the nasal cavity.

VII. RECOMMENDED OEL

8-hr TWA: 20 ppm (47.6 mg/m^3)

VIII. REFERENCES

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