Acetone Cyanohydrin

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I. IDENTIFICATION[1,2]

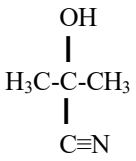
Chemical Name: Acetone Cyanohydrin

Synonyms: alpha-hydroxyisobutyronitrile; 2-propane cyanohydrin; 2-cyano-2-propanol; 2-methyllactonitrile; 2-hydroxy-2-methylpropanenitrile

CAS Number: 75-86-5

Molecular Formula: C_4H_7NO

Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1,3-7]

Physical State: Colorless liquid

Molecular Weight: 85.10

Conversion: 1 ppm (v/v) = 3.54 mg/m^3;
1 mg/m^3 = 0.28 ppm

Boiling Point: 95°C (203°F) at 760 mmHg

Vapor Pressure: 0.8 mmHg at 20°C(68°F)

Saturated Vapor Concentration: 1053 ppm at 20°C (68°F)

Odor Description and Threshold: Bitter almond (cyanide) odor can be recognized by most experienced workers at 3 ppm.

Flammability Limits: Lower explosive limit: 2.2%; upper explosive limit: 40.0%

Flash Point (closed-cup): 74°C (165°F)

Autoignition Temperature: 688°C (1270.4°F)

Specific Gravity: 0.932 at 19°C (66.2°F)

Vapor Density: 2.93

Solubility: Freely soluble in water and several common organic solvents but not in petroleum ether or carbon disulfide.

Stability: Normally unstable and readily undergoes violent chemical change but does not detonate,

Reactivity and Incompatibilities: Free hydrogen cyanide (HCN) and acetone are formed by slow dissociation of product in ambient storage. Dissociation rate increases with increasing alkalinity (pH), water content, and temperature. Lethal amounts of HCN can be present in vapor and liquid phases.

III. USES AND VOLUME

Acetone cyanohydrin is produced from the reaction of acetone and hydrogen cyanide. It is also produced from the reaction of acetone and either sodium cyanide or potassium cyanide.[1] Approximately 1.4 billion pounds of acetone cyanohydrin are produced annually by four companies in the United States. Virtually all of the acetone cyanohydrin is converted to methacrylic acid or some ester of methacrylic acid. Most production is for local captive use. About 25% is marketed.

IV. TOXICOLOGY DATA

A. Acute Toxicity

I. Oral Toxicity

Rat;	LD_{50}	17 mg/kg[8]
Rabbit:	LD_{50}	13.5 mg/kg[9]
Mouse:	LD_{50}	15 mg/kg[7]
Guinea pig:	LD_{50}	9 mg/kg[9]

2. *Eye Toxiciry*

In rabbits 0.5 mL undiluted chemical in the eye caused death. [8]

3. *Skin Toxicity*

a. frritation

In rabbits 0.01 mL in an undiluted and uncovered sample, 24-hr continuous contact. produced no irritation. [8]

b. Absorption

Guinea pig: LD_{50} 140 mg/kg[10]

Rabbit: LD_{50} 16 mg/kg[16],

4. *Inhalation Toxicity*

A 4-hr exposure to 62.5 ppm was lethal to 2/6 rats; 125 ppm was lethal to 6/6 rats. [8]

A l0-min exposure to a saturated vapor (nominal concentration ~1050 ppm) caused 50 percent mortality.[10]

5. *Intraperitoneal Toxicity*

Mouse: LD_{50} 1 mg/kg [11]

6. *Subcutaneous Toxicity*

Rat: 8.5 mg/kg [12]

B. Mutagenicity

No mutagenic activity was observed when acetone cyanohydrin was evaluated in a microbial mutagenicity assay using five *Salmonella* strains [13] or in the Chinese Hamster-Ovary mammalian cell gene mutation assay. [14] Both assays were conducted with and without metabolic activation. No mutagenic activity or chromosome damage was observed in an in vivo rat bone marrow clastogenesis assay. [15]

C. Metabolism and Pharmacokinetics

The toxic action of acetone cyanohydrin is associated with the in vivo release of hydrogen cyanide when acetone cyanohydrin dissociates into acetone and hydrogen cyanide.[10] This is supported by the effectiveness of treating cyanohydrin poisoning in rats by the administration of amyl nitrite, sodium nitrite, or sodium thiosulfate.[16]

Cyanide acts by inhibiting cytochrome oxidase and, thus, impairing cellular respiration.[17] At higher concentrations cyanide may completely inhibit cellular respiration and produce histotoxic anoxia.[18] If the concentration of cyanide ion is not so great as to cause death, then it is released from its combination with the ferric iron of cytochrome oxidase or methemoglobin, converted to thiocyanate ion (SCN^-) and excreted in the urine.[10]

D. Reproductive/Developmental Toxicity

No significant differences or trends were observed in fetuses or litters of rats administered acetone cyanohydrin by gavage at dose levels of 1.0, 3.0, or 10 mg/kg on days 6 through 15 of gestation. Only material toxicity was observed as a slight decrease in body weight gain at 3.0 and 10.0 mg/kg/day.[20]

In fertility studies, male Sprague-Dawley rats were exposed by the inhalation route (6 hr/day, 5 days/week) to acetone cyanohydrin at levels of 10.0, 28.5. and 57.2 ppm. Males were exposed for 48 exposure days and mated to untreated females. The number of live implants and pre- and post-implantation losses from females sacrificed at mid-gestation were comparable for females mated with untreated and treated males. [21]

Female Sprague-Dawley rats were exposed by the inhalation route (6 hr/day, 7 days/week) to acetone cyanohydrin at levels of 10.7. 30.4, and 58.6 ppm for 21 exposure days and then mated to untreated males to assess female fertility. Females were exposed until day of mating. At mid-gestation fertility of mated females was comparable between rats of the treatment groups and the control group for mating efficiency, pregnancy rates, number of live implants, and pre- and post-implantation losses. [22]

E. Subchronic Toxicity

A pilot study with acetone cyanohydrin was evaluated by inhalation, wherein groups of male and female rats were exposed to concentrations of 0, 9.2, 29.9. or 59.6 ppm in the air 6 hr/day, 5 days/week, for l month.[23] Irritation of the eyes, nose, or both and breathing difficulties in the mid and high exposure groups and nonsignificant decreased body weight in high exposure group of animals were noted. Signs of anoxia/hypoxia, such as respiratory distress and tremors or convulsions or both, were observed following the first exposure in four high exposure animals. Three of these animals subsequently died. Serum T_3 levels (indicator of thyroid gland function) were significantly increased in mid-exposure males; this change, however, was considered to be within biological variation for the rat and not compound-related. The no observable adverse effect level (NOAEL) for acetone cyano-hydrin was 9.2 ppm. In a further subchronic study, no significant toxicologic or pathological effects were observed when rats were exposed to acetone cyanohydrin at concentrations of 0, 10. l, 28.6, and 57.7 ppm in the air for 6 hr/day, 5 days/week, for 14 weeks.[24] Under the conditions of this test, NOAEL was considered to be greater than 57.7 ppm. Serum T_3 and T_4 levels were not different from one exposure group to the others in this study. The difference in the NOAELs between the above two studies can possibly be explained either by the very steep dose-response curve for acetone cyanohydrin or simply by the variation that exists within animals of the same strain by both. Also, there were no differences in the purity of test compounds in the two studies to account for the different NOAELs.

F. Chronic Toxicity

Groups of 50 white rats were administered orally 5 mg of acetone cyanohydrin twice a week over a period of 3, 5, or 8 months. After exposure, the animals were killed. The authors [25] found various lesions of the stomach, liver, and kidney that became irreversible with prolonged exposure. In the same study. groups of 50 white rats were administered by inhalation l mL of acetone cyanohydrin in 84 L of air twice a week over a period of 3, 5, or 8 months. Insufficient information was given to calculate the inhalation concentration or dose. Inhalation exposure produced lesions in the lung with desquamation of bronchial epithelium, progressing to superficial ulcerations associated with inflammatory infiltrations.

A study of the chronic effects of acetone cyanohydrin was conducted in 44 albino rats and 16 rabbits.[9] The animals received daily doses of 0.00005, 0.0005, 0.005, or l.33 mg/kg for 6 months and were killed at the end of the exposure period. The number and frequency of doses and route of administration were not specified. At doses of 1.33 mg/kg an increase in erythrocytes, reticulocytes, and hemoglobin; an increase in Vitamin C in the liver and adrenals; a decrease in the content of sulfhydryl groups in the brain; and a decrease in the activities of serum catalase and cholinesterase were observed in rats. At doses of 1.33 and 0.0005 mg/kg, rats exhibited functional changes in higher nervous system activity; at doses of 0.0005 mg/kg, rats showed functional changes in the morphologic composition of the blood, catalase, and cholinesterase. At doses of 1.33 mg/kg rabbits exhibited a slower utilization of galactose and a decrease in the content of sulfhydryl groups in the bloodstream. At doses of 0.005 and 0.0005 mg/kg, rabbits showed co noticeable effects in any of the tissues that were examined. At doses of 0.00005 mg/kg, neither species showed any adverse effect.[9]

V. HUMAN USE AND EXPERIENCE

Acetone cyanohydrin has been reported to be highly toxic by all routes of exposure. The effects following exposure to acetone cyanohydrin are dizziness, headache, listlessness. difficulty in breathing, rapid or irregular heartbeat or both, weak pulse, tightness or pain in chest, and loss of consciousness. Other symptoms include a heavy feeling in the limbs and joints, numbness of the upper lip, and blood-shot eyes. On contact, although there is no irritation, a brown discoloration may be observed in the area. Acetone cyanohydrin readily decomposes into hydrogen cyanide and acetone because of the alpha-hydroxy group present. Acute overexposure to hydrogen cyanide may produce rapid collapse and respiratory arrest. Symptoms following overexposure to acetone cyanohydrin are narcosis, skin and mucous membrane irritation, nausea, vomiting, feeling of unrest, collapse, intermittent breathing, and coma. [7]

The principal route of exposure to acetone cyanohydrin is dermal. Both animal studies and human exposure incidents indicate that acetone cyanohydrin is readily absorbed through the intact skin. [10]

The stability of acetone cyanohydrin is reported to be pH-dependent, with stability being greater in an acid medium.[10] At a pH of 7.4, acetone cyanohydrin may spontaneously release cyanide ions. In a case of delayed hydrogen cyanide poisoning resulting from the dissociation of acetone cyanohydrin the authors reported that perspiration on the skin provided an alkaline medium favoring dissociation.[17] The authors postulated that hydrogen cyanide easily penneates the vascular and lymphatic endothelium and is aided by the ability of acetone to dissolve lipid substances in these tissues.

An exposure to acetone cyanohydrin in which the worker had skin exposure from a splash of the compound produced symptoms of nausea 3 hr after exposure, unconsciousness. convulsions, and death 6.5 hr after exposure. In three nonfatal cases, operators who had dermal exposures lost consciousness but were revived after they were carried into fresh air and had their hands; washed.[10] Two fatalities resulted from accidental splashing on the face and clothing of workers.[26] The fatalities represent combined dermal and respiratory exposure.

The effect of chronic cyanide exposure was evaluated in an epidemiologic study involving 36 male Egyptian workers employed in the electroplating section of three factories for an average of 7.5 years. The workers were exposed to hydrogen cyanide at concentrations ranging from 4.2 to 12.4 ppm. The findings showed an increase in subjective symptoms such as headache, throat irritation, lacrimation, vomiting, aud dyspnea. Enlargement of the thyroid gland, attributed possibly to the effects of thiocyanate (the chief metabolite of cyanide), was also reported in 56% of the exposed workers.[27]

VI. RATIONALE

The National Institute for Occupational Safety and Health[28] (NIOSH) recommended a limit of 1 ppm ceiling for acetone cyanohydrin based on a 15-min sampling period. This recommendation was based on a comparison of acetone cyanohydrin lethality to acetonitrile lethality as determined in rat inhalation studies. The NIOSH acetonitrile limit was supported by a case report of an accidental group exposure to this compound.[29] However, the major difficulty in ranking nitriles on the basis of relative toxicities is that the few available inhalation values do not show the same relative toxicity as the subcutaneous injection values do.[28]

Acetone cyanohydrin will dissociate readily to yield hydrogen cyanide and acetone and behaves like its molar

equivalent in cyanide.[30] The onset of toxicity is related to the time required for dissociation to produce free hydrogen cyanide.[28] The rationale for establishing a workplace environmental exposure level (WEEL) for acetone cyanohydrin may, therefore, be based on analogy with hydrogen cyanide.

The NIOSH Criteria Document[31] recommended a 10-min ceiling of 5 ppm for hydrogen cyanide to protect against both the chronic and acute effects of cyanide exposure. The ceiling is based largely on an epidemiologic study [27] and other studies[31] reporting thyroid enlargement and throat irritation to workers exposed to hydrogen cyanide at less than 10 ppm.

The former Occupational Safety and Health Administration (OSHA) limit for hydrogen cyanide was a 10 ppm 8-hr time-weighted average (TWA) with a "skin" notation. Recently OSHA revised this limit and established a PEL of 4.7 ppm as a 15-min short- term exposure limit (STEL) and retained the "skin" notation. [32] OSHA concluded that neither its former permissible exposure limit (PEL) nor the American Conference of Governmental Industrial Hygienists[33] (ACGIH) threshold limit value (TLV®) of 10 ppm Ceiling with a "skin" notation is sufficiently protective because a variety of symptoms and effects are associated with exposure to hydrogen cyanide at levels less than 10 ppm.

One producer has set an internal limit of 2 ppm 8-hr TWA. with a "'skin" notation, to protect against the chronic effects of hydrogen cyanide exposure and a 5 ppm 15-min STEL to be consistent with the revised OSHA PEL for hydrogen cyanide. [34]

Because acetone cyanohydrin behaves qualitatively and quantitatively like its molar equivalent in cyanide, it is recommended that the limit for acetone cyanohydrin be the same as for hydrogen cyanide.

An OEL of 2 ppm 8-hr TWA is recommended to protect against chronic effects from exposure to acetone cyanohydrin. In addition, a 15-min TWA of 5 ppm is recommended to provide a margin of safety against acute poisoning. Because acetone cyanohydrin may be rapidly absorbed through the skin in lethal amounts, a "skin" notation is needed.

VII. RECOMMENDED OEL

8-hr TWA: 2 ppm (7.1 mg/m^3). Skin
15-min TWA: 5 ppm (17.7 mg/m^3), Skin

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