MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 24, 2001

TO: File for Isooctanol (CAS No. 26952-21-6)

FROM: Michael Depa, Toxics Unit, Air Quality Division

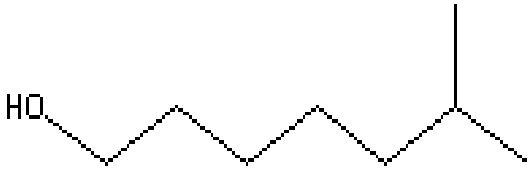
SUBJECT: Development of the Screening Level

The initial threshold screening level (ITSL) for isooctanol (also called isooctyl alcohol) is 2700 µg/m³ (8-hour averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967-September 2000), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD) for isooctanol. The ACGIH TLV and the NIOSH Recommended Exposure Level (REL) for isooctanol are 266 and 270 mg/m³, respectively.

Physical Properties

Figure 1. Molecular Structure of Isooctanol



Molecular weight: 130.23 g
Molecular formula: $C_8H_{18}O$
Boiling point range: 184-191ºC
Vapor pressure: 0.4 mmHg
Other: combustible liquid, insoluble in water

Although Figure 1 shows the molecular structure of 6-methyl-1-heptanol, the exact composition of the substance known as "isooctanol" is not certain. Both the ACGIH and NIOSH describe it as "mixed isomers." The Chemical Abstract Service, which assigns CAS numbers indicates that 26952-21-6 is an "Incompletely Defined Structure" (IDS). The RTECS does not provide synonyms that could provide clues as to the exact nature of the various isomers. The best definition available comes from the TLV Documentation for isooctyl alcohol (ACGIH, 1996), which states:

It is a mixture of closely related isomeric, alcohols consisting of 70-80% dimethyl-1-hexanols, 10-20% methyl-1-heptanols, and 5-10% other homologous primary alcohols.

Chemfinder (http://chemfinder.camsoft.com) describes isooctyl alcohol (CAS No. 26952-21-6) as 6-methyl-1-heptanol, and also provides the molecular structure for this isomer of isooctyl alcohol (Figure 1).

TLV Documentation
The ACGIH provides little oral or inhalation toxicity data on which they base the TLV. They cite an LD50 of 1.48 g/kg and state that the principal signs of effect were central nervous system (CNS) depression and labored respiration. In an inhalation study, the ACGIH states, "Mice, rats, and guinea pigs that inhaled 200 ppm (1063 µg/m³) isooctyl alcohol for 6 hours showed moderate, local irritation of the mucous membranes of the upper respiratory tract, but no signs of systemic intoxication were noted." In the derivation of the TLV, the ACGIH states that, "Animals that inhaled 200 ppm isooctyl alcohol suffered moderate irritation of the upper respiratory tract. Accordingly, a TLV-TWA of 50 ppm is recommended for isooctyl alcohol to minimize the potential for such irritation."

Animal Studies
In an acute toxicity study, the oral LD50 was calculated in Sprague-Dawley rats (Scala and Burtis, 1973). Groups of 5 were dosed by gavage and observed for 14 days. Gross necropsy was performed on all rats. The method of Litchfield and Wilcoxon was used. The LD50 was 1.48 g/kg, i.e., 1480 mg/kg.

In a 6-hr inhalation exposure of 200 ppm (1,063 mg/m³), groups of 10 mice, rats, and guinea pigs were dosed with isooctyl alcohol at nearly saturated atmospheres of vapors. The observation period was 6 hours. No attempt was made to stop droplets from forming, and analytical determination of chamber concentrations were not made. The nominal concentration was calculated from the net loss of alcohol from the bubblers and the total chamber airflow. No deaths were observed. Signs of toxicity were not pronounced and consisted primarily of central nervous system depression. Irritation of the mucous membranes was listed as "Slight-Moderate."

In a gavage study, a group of 5 male Wistar rats were exposed to 130 mg/kg/day isooctanol for 14 days (Rhodes, et al., 1984). Few toxicological parameters were examined. The authors reported that no major pathological signs of hepatotoxicity were observed. Two of 10 rats had slight centrilobular hypertrophy. Four of 10 rats had "slight/moderate glycogen vacuolation," and 3 of 10 rats had, "slight/moderate centrilobular 'fat' vacuolation." It was reported that there was no change in body weight gain, liver to body weight ratio, and testis to body weight ratio. The authors indicated that isooctanol exposure did not result in peroxisome proliferation (as shown morphometrically) and hypochloesteraemic/hypotriglyceridaemic effects. There was also no effect on catalase.

In a 2-week inhalation study, groups of 10 male CD rats were nose-only exposed to 0, 100, 600, 3100 mg/m³ for 6 hours per day and 5 days per week (Du Pont, 1985). Five rats from each group were killed after the 10th exposure, and the remaining rats after 14 days of recovery. Rats exposed to 3100 mg/m³ had frequent instances of lung noise, clear and red nasal discharge, crusty white nasal area, red ocular discharge, red stained perineum, inactivity , impaired balance, ruffled fur and alopecia. Rats exposed to 110 mg/m³ also had lung noise during exposure. Mean body weight of rats exposed to 110 and 600 mg/m³ were similar to controls throughout the study. Rats in the 3100 mg/m³ group had body weight significantly lower than control rats throughout the study. Absolute kidney weights were significantly increased in rats exposed to 110 and 600 mg/m³, and kidney to body weight ratios were significantly increased in rats exposed to 600 or 3100 mg/m³. After 14 days of recovery, spleen

weights were significantly lower on both an absolute basis and relative to body weight basis in all test groups. After the 10th exposure, rats exposed to 3100 mg/m³ had significantly increased erythrocyte counts, hemoglobin and hematocrit values, and decreased main corpuscular hemoglobin values, leukocyte counts, and absolute numbers of lymphocytes and eosinophils. At 600 mg/m³ there were increased hemoglobin and hematocrit values and decreased absolute numbers of eosinophils. The authors stated that increases in red blood cell parameters which occurred in the 600 and 3100 mg/m³ dose groups were interpreted to be evidence of treatment-related secondary polycythemia. Acute rhinitis with necrosis and squamous metaplasia of respiratory nasal epithelium were observed at the 3100 mg/m³ dose, similar but less severe effects were seen at the 600 mg/m³ dose level. The 110 mg/m³ dose level was identified as the lowest-observed-adverse-effect-level (LOAEL) based on increased kidney and decreased spleen weights as well as lung noise during exposure.

Derivation of Screening Level

The CAS definition implies that isooctanol is a mixture of isomers. The ACGIH (1996) definition of isooctyl alcohol provides a similar definition. Because of this similarity, it was deemed appropriate to use the ACGIH TLV to derive the screening level. Pursuant to Rule 232(1)c, the initial threshold screening level (ITSL) was determined as follows:

ITSL = OEL divided by 100

Where OEL is the occupational exposure level.

ITSL = 270 mg/m³ ÷ 100

ITSL = 2.7 mg/m³

ITSL = 2700 µg/m³

The ITSL for isooctyl alcohol is 2700 µg/m³ with an 8 hour averaging time.

REFERENCES

ACGIH. 1996. Threshold limit values (TLVs) and biological exposure indices (BEI) documentation. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 45240-1634.

DuPont. 1985. Subchronic inhalation toxicity of isooctanol. Haskell Laboratory Report No. 378-84 (MR No 4842-001), Newark, Delaware. The date the report was issued was June 6, 1985. This document was obtained from the EPA/OTS as microfiche: Doc# 88-920008844.

Rhodes C, Soames T, Sonard MD, Simpson MG, Vernall AJ, Elcombe CR. (1984) The absence of testicular atrophy and in vivo and in vitro effects on hepatocyte morphology and peroxisomal enzyme activities in male rats following the administration of several alkanols. Toxicology Letters. Vol. 21: 103-109.

Scala RA, Burtis EG. 1973. Acute toxicity of homologous series of branched-chain primary alcohols. American Industrial hygiene Association Journal. 34(11): 493-9.

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