MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Monoisopropanolamine (CAS #78-96-6)

FROM: Margaret M. Sadoff, Air Quality Division, Toxics Unit*

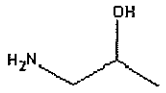
SUBJECT: Screening Level Derivation

DATE: January 4, 2008

The initial threshold screening level (ITSL) for monoisopropanolamine is 15 µg/m³ based on an annual averaging time.

A search of the literature and the following databases was performed for information regarding monoisopropanolamine (MIPA): American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, U.S. Environmental Protection Agency (EPA), Integrated Risk Information System (IRIS), EPA High Production Volume Information System, Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, National Library of Medicine ToxSeek, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, Scirus, IPCS Intox Databank and California EPA's Toxicity Values Database

Figure 1 **MW = 75**



General Information

MIPA is a clear, colorless liquid with a slight ammonia-like odor. It is highly soluble in both water and most organic materials, which makes it useful as an emulsifying agent in drycleaning soaps, soluble textile oils, wax removers, metal cutting oils, cosmetics, emulsion paints, plasticizers, and insecticides. A vapor pressure of 0.47 mmHg @ 25C indicates that MIPA will exist as a vapor in ambient air. It has an atmospheric half-life of approximately 10 hours. (Toxline HSDB; Cosmetic Ingredient Review Expert Panel, 1987).

Human Toxicity based on Occupational Data

The EPA has not established a reference concentration or reference dose for MIPA. There are no U.S occupational exposure standards for MIPA, but two foreign occupational exposure limits were listed in RTECs as:

OEL-RUSSIA: STEL 1 mg/m3, Skin, JUN2003
OEL-AUSTRIA: MAK 5.8 mg/m3 (2 ppm), JAN 2006

Hervin and Lucas (1974) published an occupational study in which 15 employees with known contact to MIPA were interviewed about their general health. Five instances of primary irritant contact dermatitis due to direct skin exposure to MIPA were identified. One individual also noted upper respiratory tract and eye irritation due to this substance. A single case presented with headache, stomach ache, sore throat and eye irritation and a history of dermatitis.

In an attempt to induce sensitization, 150 volunteers were given 48- to 72-hour covered patch tests with a 2% aqueous solution, three times per week for three weeks. After a 2-week rest period, a 48-hour challenge patch elicited no local reactions, indicating that sensitization had not occurred. In an attempt to induce photosensitization, 50 volunteers were given 24-hour covered patch tests with a 2% aqueous solution, three days a week for three weeks. After each patch removal, the test sites were irradiated with UV light. Following a 2-week rest period, each volunteer was given two challenge patches. One remained in place for 24 hours, after which the test site was irradiated with UV light and the other remained in place for 48 hours. No evidence of allergic or photoallergic dermatitis was apparent (Maibach, 1986).

Acute Animal Toxicity

One LC50 in male Fischer Rats reported as > 3460 mg/m3, 6-hour exposure, 14-day observation period, no deaths. Slightly enlarged livers were reported at autopsy (n=2/6). (DOW, 1981)

DOW also reported an LD50 in rats of 2098 mg/kg.

Six M/F rats were exposed to a highly saturated vapor-air mixture at 20C for 8 hours. No symptoms were observed and there were no mortalities. No gross abnormalities found at autopsy. [A theoretical saturated atmosphere is approximately 1100 ppm or 3370 mg/m3] (BASF, 1965)

A single dose oral toxicity test in rats with a 14-day post-test observation period resulted in an LD50 of 4.26 (3.89-4.67) g/kg. (Smyth & Carpenter, 1951).

In acute toxicity tests in mice, rabbits and guinea pigs, MIPA produced irritation of the mucous membranes of the eyes and upper respiratory tract, and central nervous system excitation followed by inhibition (RTECS).

An inhalation study was conducted by Detwiler-Okabayashi and Schaper (1996) in mice. A 3-hour exposure to an aerosol of MIPA resulted in a decrease in respiratory frequency. The exposure concentrations ranged from 230 to 1005 mg/m^3. The concentration that decreased respiratory frequency by 50% was 440 mg/m^3. Nasal and lung irritation were also observed.

Subchronic Oral Toxicity

Smyth et al. (1949) conducted a 90-day oral study in ten rats, administering MIPA through the diet at concentrations ranging from 0.14 g/kg to 2.22 g/kg. Liver and kidney weights were altered but there is little study detail given. The authors concluded that the NOAEL was 0.60 g/kg.

DOW Chemical Co. 2-week inhalation study with rats and mice (1982)

4-6/sex/group M/F B6C3F1 mice and Fischer 344 rats were whole-body exposed to 0, 25, 50, or 75 ppm (0, 77, 153, or 230 mg/m3) MIPA vapors for 6 hours per day, 5 days a week for a total of nine days. Animals were observed daily for general appearance and health. Hematology, clinical chemistry, gross pathology and histopathology were performed on all animals. In addition rats underwent urinalysis. Gross pathology included kidney, liver, brain thymus and testes gross observations and weights. Histopathology performed on tissues in all dose groups included liver, kidneys, nasal turbinates, trachea and lungs. Additional histopathology of all other major organs and glands was performed on high dose and control animals only. Appropriate statistical tests were performed and chamber conditions were well-monitored and controlled. Time weighted average chamber concentrations of MIPA were within 7% of targeted concentrations. Actual mean concentrations achieved were 30, 50 and 70 ppm.

All animals appeared normal and in good health throughout the study despite the wetted condition of middle and high dose animal fur immediately after exposure. There were no treatment related deaths during the study. Male rats in the high dose group experienced statistically significant decreased weight gain which was attributed to exposure related stress (wetting of fur and subsequent grooming afterwards may have suppressed appetite) and presence of viral disease in some of the animals. There was a uniform depression of liver weights in all groups of treated male rats which gave no clear dose-response relationship. This change was believed to be attributable to the lower rates of weight gain in these animals due to their decreased food consumption.

The authors indicate that histopathology revealed no treatment related changes but did provide evidence of an ongoing viral bronchopneumonia and rhinitis infection in many of the control and treated animals. Both mice and rats exhibited respiratory tract lesions but the incidence was generally low and not statistically different between control and treated mice. In general, the incidence of respiratory lesions in treated rats was higher than controls, but no consistent dose-response relationship was established. Although statistically elevated serum albumin and decreased total bilirubin was observed in treated female mice, they were within historical control ranges and thus were not assumed to be dose-related.

A complicating factor in the assessment was the presence of an active bronchopneumonia/rhinitis in many control and treatment animals. Presence of this virus may have exacerbated some results, especially the incidence of respiratory lesions. Rats appeared to be more affected than mice. The authors reported no exposure-related changes in any of the parameters and therefore deemed the high dose group at 75 ppm (230 mg/m^3) a NOAEL. [Actual mean exposure concentration achieved was 70 ppm or 215 mg/m3.]

Discussion

The 90-day oral study (Smyth et al., 1951) is of limited value for screening level derivation because of the small number of animals utilized, lack of experimental detail and the limited number of parameters evaluated. This study does not meet the minimum quality criteria for a 90-day study from which an RfD-based ITSL could be derived.

The short term DOW study can be used to derive an ITSL pursuant to Rule 232(1)(d). The authors reported 75 ppm or 230 mg/m3 as a NOAEL. The finding of respiratory tract changes due to viral infections complicates the analysis because the respiratory tract is a target organ of MIPA. However, this is a well-conducted study with complete histopathology, clinical and serum chemistry and gross pathology. Since the reported respiratory effects were slight to mild even with the viral infection, these results can be considered a worse-case scenario for MIPA exposure. A full factor of 35 with no reduction for the slightly longer study duration (9 vs. 7 days) and the actual mean exposure concentration attained under experimental conditions of 70 ppm (215 mg/m3) will be used to calculate an ITSL.

Dow (1982, secondary reference):

$$ITSL = \frac{NOAEL}{35 \times 100} \times \frac{\text{hours exposed per day}}{24 \text{ hours per day}}$$

$$ITSL = \frac{215\ mg/m^3}{35 \times 100} \times \frac{6 \text{ hours per day}}{24 \text{ hours per day}}$$

$$ITSL = 0.015\ mg/m^3$$

$$ITSL = \mathbf{15\ ug/m^3}$$

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*Original draft of document was completed on June 29, 2007 by Anne Kim.

Other References:

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