MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

April 28, 1993

TO: File for Dimethyl Sulfate (CAS# 77-78-1)

FROM: Mary Lee Hultin

SUBJECT: Screening Level for Dimethyl Sulfate (CAS# 77-78-1)

The following sources were searched for toxicity data:

RTECS
EPA IRIS
DNR EPB and NUTSHELL
NIOSH
ACGIH TLV
CAS Online
NLM CCRIS database

Although the database is not complete, the primary concerns with dimethyl sulfate include the irritant potential and genotoxic/carcinogenic properties. The irritating properties are evidenced from human occupational data and animal studies (ACGIH, 1990; WHO, 1985). Dimethyl sulfate has been shown to be a severe skin and eye irritant in Draize tests (RTECS, 1993).

The U.S. EPA carcinogenicity classification for dimethyl sulfate is B2; probable human carcinogen. However, EPA fails to give a quantitative estimate of risk. The Interagency for Research on Cancer (IARC) considers animal carcinogenicity data to be sufficient, but concludes there is inadequate data for human carcinogenicity classification. The World Health Organization concludes that there is insufficient data for risk assessment, but cautions that 3 mg/m3 has been shown to be carcinogenic. WHO states that dimethyl sulfate should be assumed to be a potential human carcinogen and urges that all efforts should be made to reduce exposure.

The National Institute for Occupational Safety and Health (NIOSH) lists an exposure limit of 0.5 mg/m3, gives a skin notation, and designates dimethyl sulfate as an occupational carcinogen. The American Conference of Governmental, Industrial Hygienists lists a TLV of 0.5 mg/m3 with an A2 designation as a Suspected Human Carcinogen. The Occupational Safety and Health Administration (OSHA) established a permissible exposure limit (PEL) of 0.1 ppm with a skin designation.

Human data is inadequate for determination of carcinogenicity. Druckrey, et al. reported one case of "oat cell carcinoma" of the upper bronchus

following occupational exposure to dimethyl sulfate. However, ACGIH, cites a negative occupational carcinogenicity from dimethyl sulfate exposure attributed to Thiess, et al, 1969. According to IARC, case reports raise some suspicion regarding possible human carcinogenicity of dimethyl sulfate, but epidemiological evidence is lacking.

Most of the carcinogenicity designations appear to focus on the work of Druckrey, et al. and supporting mutagenicity data. Unfortunately, the data is in German and not available for review. Citations from secondary references provide the following information:

> Druckrey, et al., treated BD rats with 10 ppm (about 55 mg/m3) or 3 ppm (about 16 mg/m3) dimethyl sulfate vapor for 1 hr./day, 5 days/week for 19 weeks. Animals were apparently observed for at least 643 days. According to the citation of this work by ACGIH, the dose levels were calculated, but unmeasured. Several early deaths from inflammation of the nasal cavity and pneumonia were reported in the high dose group. Of the surviving animals, 3 had squamous cell carcinomas of the nasal cavity, 1 developed a glioma of the cerebellum and one a lymphosarcoma of the thorax with metastases in the lungs. In the low dose group, 1 developed a squamous cell carcinoma of the nasal cavity, 1 an aesthesioneuro-epithelioma of the olfactory nerve and 1 a malignant neurinoma. Some early deaths also occurred at the low dose. The rare neurologic tumors were observed distant from the exposure site.

Druckrey, et al, also performed a transplacental carcinogenesis experiment. A dose of 20 mg/kg dimethyl sulfate was administered via i.v. to pregnant BD rats on day 15 of gestation. Offspring exhibited 4 neurogenic and 2 hepatic malignant tumors. According to the ACGIH description of the study, these tumors appeared late in the lives of the rats. However, they add weight to the neurologic tumors observed in the inhalation study.

Also in 1970, Druckrey performed a single subcutaneous injection of 50 mg/kg dimethyl sulfate and found local sarcomas of the connective tissue in 7/15 rats within 740 days of treatment. Metastases to the lung were reported in three cases. In earlier work, Druckrey, et al., (1966) injected BD rats subcutaneously with 8 and 16 mg/kg dimethyl sulfate per week for 394 and 343 days, respectively. Injection-site sarcomas were reported in 7/11 of the surviving low-dose rats and 4/6 or the surviving high dose rats. Occasional metastases to the lung were observed. One hepatic carcinoma was reported in the rats exposed to the low dose. Mean tumor induction time was reported to be 500 days. Groups of BD rats given 2 or 4 mg/kg dimethyl sulfate via i.v. for 114 weeks did not develop any tumors (Druckrey, 1970).

WHO, 1985 cites work by Schlogel and Bannasch, 1970 and 1972 in which inhalation studies were performed. Studies used golden hamsters, Wistar Rats and NMRI mice. Doses given included: 3 mg/m3 for 6 hours, twice per week or 8.7 mg/m3 every 14 days for 6 hours. The inhalation exposure was for 15 months. Malignant tumors of the nasal cavity and lung were seen in 10/74 animals at the high dose; 4/97 low dose animals had malignant tumors. The original data is in German, and thus not directly available for review. EPA, 1993, reports that results of this data are unclear due to the lack of reported control data and failure to tabulate tumor incidence by species and dose. WHO, 1985 also cites the work of Fomenko, 1983 (in Russian) in which female mice were given doses of 0.4, 1 or 20 mg/m3 dimethyl sulfate for 4 hours/day, 5 days per week. A statistically significant increase in lung adenomas was observed in the high dose group.

Although the majority of these studies found tumors primarily at the site of administration, the neurogenic tumors found by Druckrey were removed from the exposure site. None of the original data was available for review and risk assessment since it is either in German or Russian. However, despite the lack of sufficient data for risk assessment, all major organizations who have reviewed the data have determined there to be sufficient evidence to label dimethyl sulfate as a carcinogen. In addition, a number of positive mutagenicity assays lend supportive evidence. The mutagenic effects were summarized in the WHO, 1985, document: "DNA damage, mutations, chromosomal anomalies, and other genotoxic effects have been observed in viruses, prokaryotes, fungi, vascular plants, insects, fish, mammalian cells in vitro, and in mammals in vivo." According to EPA, "Dimethyl sulfate is a potent alkylating agent for cellular macromolecules."

ITSL DERIVATION:

Although the ACGIH considered the work of Druckrey, et al. when deriving the TLV, they indicate that there is likely "a threshold considerably above 1 ppm". Evidence is insufficient at this time either to prove that dimethyl sulfate acts via a threshold mechanism, or to derive such a threshold. In addition, a significant body of mutagenicity data exists suggesting that a threshold may not be appropriate. Therefore, an additional safety factor has been added to the equation for deriving a screening level from an occupational exposure level.

TLV = 0.5 mg/m3
ITSL = (0.5 mg/m3 / 100 x 10) = 5 x 10^{-4} mg/m3 or 0.5 ug/m3 based on 8 hr. averaging

REFERENCES

1. ACGIH, 1990, Documentation of Threshold Limit Values.
2. World Health Organization, 1985, Environmental Health Criteria, #48, Dimethyl Sulfate.
3. Registry of Toxic Effects of Chemical Substances, 1993.
4. USEPA, 1993, Integrated Risk Information Service (IRIS) database.
5. Druckrey, H., et al., 1970, Zeit. f. Krebsforsch., "Cancerogene alkylierende Substanzen. III. Alkyl-halogenide, -sulfate, -sulfonate und ringgespannte Heterocyclen." v. 74:241-270 (in German), as cited in ACGIH, 1990, EPA, 1993 and WHO, 1985.
6. Druckrey, H., et al., 1966, Zeit. f. Krebsforsch., v. 68:103. (in German), as cited in ACGIH, 1990; EPA, 1993 and WHO, 1985.
7. International Agency for Research on Cancer, 1974, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, v. 4, p. 271-276.
8. International Agency for Research on Cancer, 1987, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Supplement 7, p. 200-201.