MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

December 13, 2005

TO: File for dimethyl sulfoxide (CAS #67-68-5)

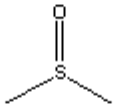
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for dimethyl sulfoxide is 20 µg/m³ based on an annual averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for dimethyl sulfoxide. The molecular weight of dimethyl sulfoxide is 78.1 g. The molecular structure of dimethyl sulfoxide is shown in Figure 1.

Figure 1



Background

Dimethyl sulfoxide (DMSO) is a clear colorless liquid that can be absorbed rapidly through the skin. DMSO is mainly used as a solvent in a wide variety of applications because of its amphipathic chemical property (where DMSO is simultaneously hydrophilic and lipophilic). DMSO is broken down into two metabolites in the body: dimethyl sulfdioxide ($DMSO_2$) and dimethyl sulfide (DMS). $DMSO_2$ is excreted by the kidney and DMS is excreted by the lungs. (ChemFinder, 2005; Santos, 2003; Yellowlees, 1980)

Animal Toxicity

The lowest oral LD50 value available is 14500 mg/kg body weight in Sprague-Dawley rats (Fisherman et al., 1969).

Caujolle et al. (1967) conducted a series of toxicity tests on a number of animals. Acute, chronic, and developmental toxicity experiments were conducted in several animal species. More specifically, acute toxicity tests were conducted using mice, rats, rabbits, and dogs; chronic toxicity tests were conducted using mice and rats; developmental toxicity tests were conducted in fowl, mice, rats, and rabbits. The report of methods and results lacked details, thus analysis of the study is limited. In addition, a discussion following the paper pointed out its faults and identified reasons for dismissing the significance of the study's results altogether.

The chronic effect of DMSO was tested in rhesus monkeys by Vogin et al. (1970). The animals were exposed for 18 months to 1, 3, or 9 mL/kg body weight of 90% DMSO by oral or dermal administration. The number of animals in each dose group was 4 monkeys in the 1 and 3 mL/kg dose groups and 6 monkeys in the 9 mL/kg dose group. There were 3 monkeys each in the oral control group and the dermal control group. A number of endpoints were recorded and analyzed such as results from biochemistry, hematology, histopathology, and gross pathology tests. The outcome of these results, however, showed little or no effect in all dermal dose groups and the two lower oral dose groups; nothing was found to be abnormal or unremarkable compared to the control group. All monkeys in the highest oral dose group, 9 mL/kg, died from emphysema and atelectasis – atelectasis is pulmonary collapse due to failure of alveoli expansion or failure to resorb air from the alveoli – except for one that perished from self-strangulation. The investigators concluded that "it is evident that rhesus monkeys can tolerate DMSO administered daily for approximately 18 months at doses up to 9 mL/kg dermally or 3 mL/kg orally, without frank evidence of intolerance" (Vogin et al., 1970).

Fishman et al. (1969) conducted a series of toxicity tests exposing male Sprague-Dawley rats by inhalation to DMSO at concentrations ranging from 200 mg/m^3 to 2900 mg/m^3. A series of acute inhalation studies were conducted varying either by dose of exposure (concentration and duration) and/or by time of terminal sacrifice. A subchronic inhalation experiment was conducted exposing a total of 32 rats to a concentration of 200 mg/m^3 7 hours per day, 5 days per week for 6 weeks. The parameters evaluated and analyzed included gross observations, hematologic endpoints, biochemical endpoints, and histopathologic examination of tissue samples. More specifically, the investigators recorded the following:

1) signs of diarrhea, lacrimation, dyspnea, ataxia, anorexia, and unusual behavior;
2) hemoglobin concentration, packed erythrocyte volume as expressed by the microhematocrit, and total leukocyte and reticulocyte counts;
3) histopathologic examinations from sections of the heart, lung, liver, spleen, and kidney; and
4) serum urea nitrogen concentration, activities of serum glutamic-oxaloacetic and glutamic-pyruvic transaminases, liver lactate concentration, activity of alkaline phosphatase in the liver tissue.

Adverse changes were observed in the acute toxicity experiments only including elevated levels of urea nitrogen in serum and pulmonary edema. Nevertheless, no change was attributed to DMSO exposure by the study investigators. Fishman et al. explained these changes by noting that the animals acutely exposed to DMSO were exposed both by the inhalation and dermal routes. They report that in their "high level experiments, there was significant 'wetting out' of the material on the animals and, as would be particularly true with DMSO, absorption through the skin may have played a major role in the total dose which the animals received" (Fishman et al., 1969). In the

subchronic study, no significant adverse effects were seen in the 32 male rats exposed to DMSO for 6 weeks. A garlic-like odor was detected on the breath of the rats following the first day of exposure to DMSO, and the hair turned a yellowish color after being exposed for a full week. The weight gain was similar to control as well as the biochemical and hematologic results. Nonspecific inflammatory changes were found in the lungs and livers of most all exposed rats, however, they were also widely found in controls.

Human Toxicity

DMSO, as previously mentioned, is a solvent used for a variety of solutes. Of them, drug compounds dissolved in DMSO have been a source of exposure in humans. In fact, DMSO itself has been used as a drug for treating a number of symptoms or diseases, such as arthritis, cerebral edema, amyloidosis, scleroderma, and interstitial cystitis (Santos et al., 2003; Yellowlees et al., 1980). Several adverse effects from DMSO use have been observed; they include "nausea, vomiting, diarrhea, hemolysis, rashes, renal failure, hypertension, bradycardia, heart block, pulmonary edema, cardiac arrest, and bronchospasm" (Santos et al., 2003). The trademark of DMSO exposure is a garlic-odor breath that is caused by the excretion of the metabolite, DMS.

A clinical case history was reported by Yellowlees et al. (1980). A husband and wife were treated for arthritic knees with intravenous DMSO infusions of 100g of 20% DMSO in dextrose solution for three consecutive days every few months. The first course of treatment was given May 1979 with no adverse symptoms in either husband or wife. In February 1980, however, after the first day of treatment, the wife showed symptoms of vomiting and cramps. After the second day of DMSO infusion, she was hospitalized for symptoms of drowsiness and vomiting blood. The husband only showed symptoms of vomiting after the second day of DMSO treatment which was controlled by subscribing prochlorperazine. On admission, the wife was drowsy yet well-oriented, and she showed signs of mild jaundice and a flapping tremor. (At the time of admission, the husband was also admitted because of his symptoms of jaundice.) Her breath had the characteristic garlic odor from DMS excretion. Soon after observing normal clotting times, her clotting times quickly shortened. Ten hours after admission, she showed signs of oliguria (scanty urination) for which she was treated. By 18 hours after admission, she was not oliguric, but she continued to show the original symptoms of drowsiness and, what was now, a coarse tremor. Twenty hours after admission, she experienced a temporal state of unconsciousness. In an attempt to remove DMSO, peritoneal dialysis was initiated the day after admission. This treatment did not appear to be effective since the characteristic smell of DMS was absent from the dialysate; hence she was removed from dialysis treatment. Over the period of 7 days while admitted in the hospital, biochemical and hematological tests were performed on blood samples from both husband and wife. Now, even though the outward clinical symptoms were dramatically different, the results from the blood tests were surprisingly similar: hemoglobin concentrations fell, liver enzyme concentrations increased, and urea and creatinine levels were high. Both patients were in good health after 7 days at which time they were discharged from the hospital. The investigators concluded that, by evidence from these two clinical cases, DMSO given intravenously is "potentially dangerous and that it should not be used for the treatment of arthritis" (Yellowlees et al., 1980).

Carcinogenicity

The carcinogenicity of DMSO has scarcely been studied, and with the few reports available in literature, there is an insufficient amount of evidence detailed to fully evaluate the carcinogenic effects from DMSO exposure.

Discussion

Although DMSO has been a widely used chemical for a number of years, its toxicity has not been extensively studied. The human clinical history case report is not useful for determining an initial threshold screening level (ITSL); it is, however, useful in supporting known and presenting new examples of DMSO-induced symptoms and effects. Of the animal toxicity studies mentioned above, one was disqualified (Caujolle et al. study), one was an oral study in monkeys (Vogin et al. study), and the other was an inhalation study in rats (Fishman et al. study).

The latter two studies can potentially be used to derive an ITSL for DMSO, however, reference to Rule 232(1) must be made, which lays out the hierarchal resources from which ITSLs should be calculated (Rule 232(1)(a-i)). The use of a short-term, oral, no-observed-adverse-effect level is listed under subrule (e), whereas the use of a short-term, inhalation, no-observed-adverse-effect level is listed under subrule (d). Therefore, the derivation of the ITSL will be based on the results of the 6-week inhalation study conducted in rats (Fishman et al., 1969).

The no-observed-adverse-effect level (NOAEL) is defined by EPA (1994):

> [NOAEL is] an exposure level at which there are no statistically and biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Some effects may be produced at this level, but they are not considered as adverse, nor immediate precursors to specific adverse effects.

There were no significant toxic effects at 200 mg/m^3 which was the only exposure concentration used in the subchronic inhalation study conducted by Fishman et al. (1969). Therefore, a NOAEL of 200 mg/m^3 will be used to derive the ITSL for DMSO.

NOTE: Rule 232(1)(d) gives an equation for use of a NOAEL derived from a 7-day inhalation study. The use of a 6-week subchronic study with this equation suggests a possible reduction in the uncertainty factor of 35 which accounts for study duration. Counter balancing the possible reduction in this factor are the shortcomings of the 6-week study which include use of a single dose group and histopathological examination of a limited number of organs. Considering all of the above, the uncertainty factor of 35 was not reduced.

Derivations of Screening Level

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

>where NOAEL = no-observed-adverse-effect level

Note NOAEL & hours exposed per day:
NOAEL = 200 mg/m^3 from Fishman et al. (1969)
Hours exposed per day = 7 hours from Fishman et al. (1969)

$$ITSL = \frac{200\ mg/m^3}{35 \times 100} \times \frac{7 \text{ hours per day}}{24 \text{ hours per day}}$$

$$ITSL = 0.0167\ mg/m^3$$

$$ITSL = 16.7\ ug/m^3 = \mathbf{20\ ug/m^3}$$

Therefore, the ITSL for dimethyl sulfoxide is 20 ug/m^3 based on an annual averaging time.

References

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