MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 10, 2003

TO: 2,6-difluorobenzamide file (CAS # 18063-03-1)

FROM: Gary Butterfield

SUBJECT: Screening level for 2,6-difluorobenzamide

2,6-Difluorobenzamide is a white powder with a molecular weight of 157.12 g/mol.

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 (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - May 2003), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on May 5, 2003. There were few hits found during the literature searches for toxic effects of this chemical. 2,6-Difluoro-benzamide is a metabolite of the insecticide/pesticide diflubenuron (CAS # 35367-38-5). The majority of hits were for ability for chemical analysis in different media, or half-life estimates for various media and biologic tissues.

The literature search found only three unpublished acute studies, two oral (Eli Lily 1982, EPA OTS doc. # 0544966, and Bayer 1984, EPA OTS doc. # 0543293) and one inhalation (Bayer 1984, EPA OTS doc. # 0543293), which have been submitted to EPA for TOSCA that could potentially be used to set a screening level.

A summary of another unpublished acute oral rat study was provided by Dow Chemical (Lackenby 1985). However, this study had only 3 rats per dose level and no actual LD50 was determined. Groups of three male Sprague-Dawley rats were administered 500, 1000, 2000, 4000 or 8000 mg/kg. The rats were observed for seven days following administration. Three deaths occurred, one in each of the 2000, 4000 and 8000 mg/kg dose levels.

In the acute study by Eli Lily (1982), a single group of 5 male and 5 female F344 rats was administered 500 mg/kg. There were no deaths recorded in this study at the dose level used, thus an LD50 was not determined.

In the acute oral study by Bayer (1984), groups of 5 Wistar rats were administered single oral doses of 2,6-difluorobenzamide dissolved in propylene glycol (PEG e400). The LD50 was reported to be greater than 5 g/kg for males and 3299 mg/kg for females.

In the acute inhalation study (Bayer 1984), groups of 5 male and 5 female Wistar rats were exposed by head only exposure to an atmospheric dust at a concentration of 2100 mg/m3, which was the highest concentration that could be generated. There were no deaths observed in this study. The size of the aerosol was 16.2 um MMAD with a standard geometric deviation of 1.8. The authors noted the particles were rather large. Only 4% of the generated aerosol was reported to be less than 5 um in diameter, making it somewhat questionable as to exactly how much of the exposure aerosol was actually respirable, and able to have any biologic impact.

The best study upon which to base the ITSL is considered to be the female rat oral LD50 from Bayer (1984), where an actual LD50 was determined. Usually, the acute inhalation study would be selected as the best basis for setting the ITSL over acute oral data. However, in this case, the very large particle size and no effects/deaths being observed raises questions regarding the validity of this test as a measure of acute inhalation toxicity.

Because of the questionable validity of the acute inhalation toxicity test in Bayer 1984, the next best available data for developing an ITSL is the acute oral toxicity data from Bayer (1984). This study also indicates that female rats are more sensitive than male rats. The Dow/Lackenby study did not test both sexes of rats. The single dose levels used in the Eli Lilly (1982) were well below levels where mortality occurs, and inadequate for establishing an ITSL. Considering this information, the ITSL will be based on the female rat LD50 and calculated from the equation in R232(1)(h) as follows.

$$\text{ITSL} = \frac{(3299\ \text{mg/kg})}{500 \times 40 \times 100 \times 0.167} \times \frac{1}{0.9} = 11\ \text{ug/m3 annual average}$$

The rat default inhalation rate of 0.9 m3/kg was used in the above calculation.

It should also be noted that 2,6-difluorobenzamide is a solid at ambient temperatures, and would therefore be expected to be emitted to ambient air as a particulate. The contribution of airborne 2,6-difluorobenzamide concentrations to ambient particulate levels should be considered when evaluating compliance with any of the NAAQS for particulate matter.

References:

Bayer. 1984. 2,6-Difluorobenzamide (intermediate for SIR 14591) industrial toxicity studies. Bayer rept. # 12741. EPA OTS 0543293.

Lackenby. 1985. 2,6-Difluorobenzamide acute oral and dermal toxicity, skin and eye irritation studies. Technical report number DET-0653. HERL file # DR-0140-3594-001. A summary was submitted to DEQ Air Quality Div. by Dow Chemical.

Eli Lily. 1982. ACUTE RAT ORAL TOXICITY STUDY WITH 2,6-DIFLUOROBENZAMIDE. EPA/OTS NTIS/OTS0544966.