UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**MEMORANDUM**

SUBJECT: SULFURYL FLUORIDE. ID 078003. Review of a Protocol for a Rat 2-Year Chronic Toxicity/Oncogenicity Study, Including Neurotoxicity Testing to Satisfy Guideline 82-5 (Subchronic Neurotoxicity Testing in Rat).

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**CONCLUSIONS:**

TB-I has reviewed the submitted protocol for a 2-year chronic toxicity/oncogenicity study in rat including subchronic neurotoxicity testing. Rats would be exposed by inhalation to sulfuryl fluoride at doses of 0, 5, 20 or 80 ppm (6 hr/day, 5 days/week, whole-body exposure) for 2-years with a satellite group sacrificed after about 1 year of exposure. The protocol described a standard inhalation chronic/oncogenicity study in rat.

Neurotoxicity parameters are to be examined in this study for purposes of satisfying Guideline 82-5 to supplement the previously submitted 90-day study (MRID 408399-02). Parameters to be tested include a complete functional observational battery including fore- and hind-limb grip strength and landing foot splay; and motor activity testing (48-minute session), at 3, 6, 9 and 12 months. Neurohistopathology on 5 animals of the satellite group would be processed with special staining to examine microscopic integrity of neural tissue as outlined in Protocol Amendment #2.

Overall, the study design appeared adequate for subchronic neurotoxicity testing as well as chronic toxicity/oncogenicity testing in rat. However, TB-I has the following comments on the study protocol:

1. The FOB and motor activity testing should be conducted at least once prior to 3 months during exposure (at 1 and/or 2 months). Not exposing animals on the days of neurotoxicity functional testing is acceptable.

2. Measuring of number of rears, air righting, body temperature should also be performed during the FOB.

3. Motor activity should approach asymptotic levels by the last 20% of the test session, according to Addendum 10 guidelines for neurotoxicity testing.

4. The protocol did not provide detailed listing of the brain regions, spinal cord sections or peripheral nerves to be examined; a thorough examination of representative sections should be performed.

5. Ophthalmologic examinations should be conducted at termination as well as pretreatment.

6. Whenever possible, the same animals should be used for each bleeding.

In the event that the above issues (particularly 1-4) are not resolved in the study report, the acceptability of the study will be determined upon review and in consideration with previously received data on sulfuryl fluoride.

**ACTION REQUESTED:**

On October 6, 1993, DowElanco submitted for comment a protocol for a 2-year inhalation chronic toxicity/oncogenicity study in Fischer 344 rats for sulfuryl fluoride. The protocol included neurotoxicity testing at subchronic times. This was incorporated into the study design to provide additional information for upgrading a previously submitted (Core-supplementary) subchronic neurotoxicity study in rat (MRID 408399-02; reviewed in HED Doc. 9479). The 2-year inhalation study with neurotoxicity testing has already been performed; however, the protocol was submitted to determine if it (together with the previously conducted 90-day neurotoxicity study) was adequate for satisfying the subchronic neurotoxicity data requirement for sulfuryl fluoride.