

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

JAN 27 1984

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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THRU:

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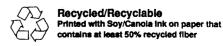
Section IV, Tox. Branch I

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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 foreand 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 quidelines 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.