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

11-27-81

MEMORANDUM

DATE: NOV 27 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Toxicology Branch Response to PROWL (Pendimethalin) Audit of Rat and Mouse Oncogenicity Studies and Assignment of Core Classification to these Studies.

TOX Chem No. 454BB

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Background:

The registrant previously submitted rat and mouse oncogenic studies and these were reviewed by Dr. R. Engler (see Engler memo dated 2/22/75 concerning pesticide petitions 5G1556, 5G1567, and 5G1580). No Core assignment was made at the time this review was conducted. Dr. Adrian Gross requested that these studies be audited and Mr. Larry Chitlik visited the Bio/dynamics Laboratory for that purpose.

The rat chronic feeding and oncogenic study and the mouse oncogenic study have been rereviewed in terms of the results of the audit and for assignment of Core classification, and for their suitability in meeting EPA's requirement for oncogenic testing.

The identification of the chronic feeding/oncogenesis studies under consideration for this chemical are as follows:

1. An 18-month carcinogenicity study of AC 92,553 in mice.

   Bio/dynamics, Project No. 72R-747, April 2, 1974.

2. A three and twenty-four month oral toxicity and carcinogenicity study of AC 92,553 in rats.

   Bio/dynamics, Inc., Project No. 72R-746, August 21, 1974.

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Conclusions:

The studies are Invalid and additional oncogenic testing is required to support registrations and petitions for the use of pendimethalin. Any future oncogenic study must use the commerical grade of pendimethalin.

The assignment of an Invalid classification is based on the following:

1. In the initial 5-6 months of the studies (both rat and mouse), a "high purity" grade of test substance was utilized. The later months of these studies utilized a technical or commercial grade of substance. Nitrosamines were present in the commercial grade but not in the "high purity" grade. Thus, the animals were not exposed to the potential carcinogens during the critical periods of growth and development. (See H. L. Avallone memo dated 5/12/80 regarding the laboratory audit.)

2. There was no data submitted for either of these studies which presented the gross necropsy findings for all of the animals inspected. Thus it could not be determined if gross lesions were followed up histologically in an acceptable manner.

3. For both the rat and mouse studies, only a very limited number of rats or mice were scheduled to be given a "complete" histopathological examination. For example, only 10 rats/sex/dose and only 15 mice/sex /dose were examined. Moreover, all of these animals were survivors and no rats or mice dying while on the study were examined histologically. In the rat study, the audit revealed that only 5 of 10 randomly selected animals had complete sets of slides--even though these animals were reported to have complete sets of slides. In the mouse study, although examination of 15 animals was called for, inspection of Appendix D of the final report indicates that only as few as 3-4 adrenals were actually examined. For other tissues, only 10-11 were actually examined. Numerous masses and lesions grossly observed in other animals were not followed up by histological examination.

   The failure to examine animals which died while on study prevents an evaluation as to whether or not the test chemical caused an earlier development of neoplasms.

   NOTE: Items 2 and 3 might possibly be corrected by submission of the raw data and appropriate tables made for the gross necropsy observations and by extensive preparation and examination of additional slides. However, item 1 is a deficiency that cannot be corrected in this manner.

   New oncogenic studies will be required to support future registrations and tolerances for this chemical in which the increased incremental exposure and/or risk is judged to be significant.

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