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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Malathion Chronic/Oncogenicity and
Ocular Effects Testing Requirements

TOX Chem No.: 535

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Pursuant to HED's Toxicology Branch I (Tox Branch) meeting of March 21, 1991 with representatives of American Cyanamid and Cheminova to further discuss malathion testing requirements, Tox Branch has determined that the malathion registrants should be advised to proceed without delay the initiation and completion of the following studies: a malathion chronic/oncogenicity study in the F344 Rat, a malathion oncogenicity study in the B6C3F1 mouse and a malaoxon chronic/oncogenicity study in the F344 rat. These requirements previously have been made known to the registrants, most recently via the Tox Branch memorandum dated September 7, 1990. Also, protocols for these studies submitted by American Cyanamid were commented upon in the Tox Branch memorandum of February 8, 1991.

Following the meeting with American Cyanamid and Cheminova representatives in March, Tox Branch scientists have independently reexamined the 1980 Food and Drug Research Labs' chronic toxicity study of malathion in the Sprague-Dawley rat. As a consequence of that reexamination which supports prior HED positions, Tox Branch here reaffirms that regardless of the outcome of the review of the results of the rereading of the histopathology slides in that study, another chronic/oncogenicity study of malathion, run by contemporary methodology and standards remains a requirement. Toxicology Branch feels this to be a particularly compelling decision in view of the resolve with which the HED Carcinogencity Peer Review Committee determined that the study was necessary (see April 12, 1990 peer review minutes).

With respect to dosage levels and duration of testing in the mouse oncogenicity study, Tox Branch has considered the registrants' request to run the study for a full two years at dosage levels not exceeding the limit dose. Tox Branch has concluded that the study should be conducted at the two high doses (exceeding the limit dose) previously indicated and for the period of 18 months. The third low dose proposed in the registrant's protocol is appropriate for inclusion. Tox Branch considers that the study should be run for the same time interval and at doses equivalent to those used in the 1978 NCI study in order to properly address the question of liver tumorigenicity identified in that earlier study. Performing the study at the same dosage levels as employed in the NCI study is considered more imperative than limiting the study to 18 months duration.

Tox Branch is of the persuasion that there should be an expeditious resolution of the malathion chronic toxicity/oncogenicity questions, and there should be no further delays in the commencement of any of these three long-term studies.

The registrants should also be advised that there remains in effect a requirement for a chronic toxicity study in the dog, designed to assess the potential ocular effects of malathion (see the relevant Tox Branch March 20, 1991 memorandum). As a consequence of recent Agency/OMB deliberations, in those cases where the one-year chronic toxicity study in the dog has been satisfied, excepting the ocular effects component, OPP may only require a 6-month dog study to satisfy the need for ocular effects testing. Hence, malathion registrants should be advised that OPP is not in the position to require that the ocular effects testing in the dog exceed 6 months' dosing. The registrants should submit a protocol for such ocular effects testing using as a guide those procedures discussed and handed out by Dr. Robert Zendzian at the March 21, 1991 meeting with the registrants (appended). Even though unique ocular effects

testing is not being required explicitly for the chronic/oncogenicity rat studies, the registrants should be advised to observe/examine test animals very closely for possible visual system effects in these studies.

As advised at the March 1991 meeting, the requirement for a 90-day inhalation study in the rat remains in effect.

As it relates to the above testing requirements, Tox Branch has read a faxed copy of a May 2, 1991 letter from American Cyanamid Company covering the "Joint Meeting of the Malathion Reregistration Task Force with EPA on March 21, 1991," accompanied by a four page enclosure. Tox Branch does not consider the information and analysis provided therein of sufficent merit to prompt changes in the study requirements as reiterated above.