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

5/6/92

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 635. Fonofos. Additional Correspondence on Acute and Subchronic Neurotoxicity Testing Protocols and Request for Deferral on Ocular Effects Testing

DP Barcode: D176286
Submission: S414961
Tox. Chem. No. 454B

TO: Joanne Edwards, PM Team # 73
Special Review and
Reregistration Division (H7508W)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 4/9/92
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C)
Roger Gardner 4-20-92 KB 5/6/92

Background and Request:

In response to a Data Call-In Notice on Fonofos dated 11/18/91, ICI Americas Inc. had submitted a proposed protocol for the neurotoxicity screening battery, acute and subchronic studies in rats. At that time, the Toxicology Branch (TB-I) reviewed and commented on the protocols. In addition, we were requested to recommend a GLP accredited laboratory able to perform a validated assay of brain neurotoxic esterase in the rat. In the same memorandum, we provided a comment on this question as well. For this action, the same requests were submitted to TB-I as well as a request for a deferral/moratorium on the ocular effects testing requirement until a clear rationale has been declared for these tests and until test guidelines are consolidated and published.

Toxicology Branch Response:

For this action, TB-I will repeat the comments provided in our previous memorandum on the submitted protocols and on the recommendation of a GLP-approved laboratory. In addition, we will address the request for a deferral of the ocular study on Fonofos until the official guidelines are published.

TB-I has reviewed the submitted protocols and has the following comments:

- The Registrant is reminded that TB-I cannot officially approve submitted protocols. We can only offer suggestions and recommendations.

- The submitted protocols for an acute and a subchronic neurotoxicity study in rats generally follow the new guidelines recommended by the Office of Pesticide Programs (OPP), and therefore, TB-I has no objections to them.

- The following points are comments and reminders concerning the protocols:

  In the acute study, the protocol did not specifically state whether or not a vehicle control was going to be used. A vehicle control group is required. In addition, if the vehicle is a known neurotoxicant, then the guidelines require both an untreated and a vehicle control group.

  In determining the dose levels to be tested, the highest dose tested (HDT) in the acute study may be a bench mark dose (i.e., highest non-lethal dose). Then the lowest dose tested may by 1/4 the HDT and the mid-dose may be 1/2 the HDT. In other words, it is desirable to have equally spaced dose levels with an underlying rationale that will maximally support detection of any dose-response.

  The protocols state that the functional observational battery (FOB) may be conducted either outside or inside the animal room. The Guidelines recommend that the FOB should be conducted at the same time of day in one standard place. It would be more appropriate to conduct the battery outside of the animal room because the smell and the sounds in the animal room may be distracting.

  For the neuropathology examinations, it is suggested that a section from the mid-thoracic region of the spinal cord be examined as well.

- Two deviations are noted that need to be addressed:

  First, the guidelines recommend the use of positive controls unless current historical control data are available with the same strain of animals tested under the same conditions in the same laboratory as the animals in the proposals. The proposals did not state whether or not historical positive control data were going to be used. TB-I suggests that positive control groups be included in the studies unless appropriate historical positive control data are available.

Second, the subchronic study proposal states that brain acetylcholinesterase (AchE) and neurotoxic esterase (NTE) assays will be conducted. The OPP guidelines do not require these assays in the rat studies; they are required in the hen studies. TB-I has no objection to adding these assays to the rat study. In fact, adding these assays to the rat study may be helpful because according to the Agency's files, the histopathology data from two of the hen studies (one acute and one 90-day), although negative, was not completely clean.

- The Agency cannot recommend testing laboratories because we are a government agency and it would be considered to be a conflict of interest to do so. Since the NTE assay is not required in the neurotoxicity testing guidelines in rats, OPP has no information on GLP accredited testing laboratories which can perform a validated assay. However, TB-I suggests that the Registrant choose a laboratory that is able to conduct the same assay in the hen. TB-I has no objections to the Registrant's choice of the world expert who was the original scientist to develop the method as the laboratory to perform the assay, although the laboratory itself is not GLP accredited.

- TB-I has no objections to a deferral of the ocular testing requirement until further guidance is provided by the Agency.