REVIEWER

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

OCT 31 1985

SUBJECT: EPA File Number 10308-1: Tetramethrin-Addendums to Pathology of the rat testis report (Vesselinovitch and Ito, July 27, 1984), exposure assessment (Edwards June 18, 1984) and risk assessment (Carlborg report July 21, 1984) and current status summary (October 1985) of studies with technical grade tetramethrin.

TOX CHEM No. 844

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TO: T.A. Gardner, PM #17
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THRU: E.R. Budd, Section Head
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Budd 10/31/85 10/31/85

Previous reviews from Toxicology Branch (TB) have indicated that tetramethrin is associated with increased incidences of neoplasms in the testis of rats. The first review (see J. Doherty memo dated April 11, 1983 for EPA Reg No. 10308-1) discussed the results of two studies conducted at Hazleton Laboratories in 1974 and in 1981. The first study conducted with Sprague-Dawley rats (males and females) showed a positive response among the males for increased incidences of testicular adenomas for both dosage level test groups receiving 3000 and 5000 ppm of tetramethrin. The second study was designed to confirm or otherwise clarify the finding of the first study and consisted of males only of both the Sprague-Dawley and Long-Evans strains of rats. The later study showed that dosing rats at 5000 ppm resulted in increased incidences of the same type of testicular interstitial cell adenomas as in the first study. Thus, potential neoplastic effects of tetramethrin were confirmed in independently executed studies.

These studies were assigned CORE classification as RESERVED and additional information was requested of the sponsor. (see review dated April 11, 1983). In particular the sponsor was

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requested to:

i. provide individual animal pathology sheets which show gross necropsy observations and microscopic findings for each rat for both the 1974 and 1981 studies;

ii. provide a table listing the exact number of rats examined microscopically for each tissue type for both the 1974 and 1981 studies;

iii. provide for the 1981 study, a comprehensive table of non-neoplastic findings for all tissues examined together with the exact number of rats examined for each tissue type.

iv. provide a table indicating the week of death of each rat for both the 1974 and 1981 rat studies together with the number of rats at risk at each week.

This information has not yet been provided by the registrant Until the above information has been provided CORE classification of these studies cannot be assigned. Registration Division (RD) is requested to again ask the sponsors to submit this information to EPA.

TB also indicated other problems related to certain other studies as follows (important: see also pages 5 and 6):

i. Dog 6-month feeding study. CORE classification of this study is still RESERVED (since April 11, 1983). The registrant must submit an addendum to this study that was referred to in a letter from E.J. Gerberg to F.D.R. Gee dated April 26, 1982. RD is requested to again ask the sponsor to submit this addendum to EPA.

ii. Mouse oncogenicity study. The pilot study designed to assess the dose levels to be used in the mouse oncogenicity study was reviewed (April 11, 1983) and it was indicated that tetramethrin has effects on several endocrine glands at dose levels of 500 ppm (lowest dose level tested) and above. Inspection of correspondence between the Sumitomo Chem. Co. and the Hazleton Laboratories revealed that the mouse oncogenicity study was initiated in January of 1982 and was expected to be completed by October of 1984. EPA has not yet received this study.

iii. Multi-generation reproduction study. The experimental design of the reproduction study (Hamamatsu Seigken Research Lab., June 14, 1980) was not consistent with conventional protocols for assessment of reproductive effects. A new study will have to be designed and conducted to fulfill this data requirement for registrations requiring a multigeneration reproduction study. See review dated February 29, 1984.

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The registrant has not resolved the problems related to these studies or provided the mouse oncogenicity study.

In a later submission (see J. Doherty review dated Feb. 29, 1984 for EPA File No. 10308-1) the registrant responded to some inquiries made by TB in the form of an addendum to the pathology report (Vesselinovitch and Ito report). This report, however, did not allow TB to dismiss the findings of testicular adenomas noted in both rat studies. In addition, TB made several comments on the Vesselinovitch and Ito report regarding classification of lesions and the number of rats available per group.

In this most recent submission, the registrants have provided additional comments on the pathology report by their consultants (Vesselinovitch and Ito report dated July 27, 1984), as well as revised exposure data and comments from a statistical consultant regarding risk assessment (Carlborg report).

The following is TB's response to the seven items which Vesselinovitch and Ito address in their addendum:

1. Classification of tissue lesion in the testis.

The original comment which the addendum refers to was included in the TB memo of February 29, 1984 in order to clarify the classification of lesions in the testis. TB did not intend to include "diffuse hyperplasia" and "nodular hyperplasia" as neoplastic lesions and TB based its neoplastic conclusions for these studies using the lesions described as "adenoma".

The comments made by the consultants in the July 27, report regarding "progression" of hyperplastic tissues are of interest but not directly related to the regulatory aspects of tetramethrin.

2. Data on diffuse hyperplasia.

TB acknowledges receipt of the table depicting the incidences of diffuse hyperplasia.

3. Reclassification of lesions by Vesselinovitch and Ito from the original Hazleton report.

TB will accept the readings made by Vesselinovitch and Ito in their report of August 13, 1983.

4. Number of control rats in the 1974 Sprague Dawley study.

TB acknowledges the changes made with respect to the number of control rats in the 1974 Sprague-Dawley study. For example, there were 50 control rats and not 40 as indicated in the Vesselinovitch and Ito report of August 13, 1983.

5. Use of Hazleton's historical control data.

TB acknowledges receipt of the comments made regarding the historical control data. TB notes, however, that although the incidences of adenomas found in the high dose test groups may be shown to be within historical control ranges, a potential neoplastic response to tetramethrin cannot be dismissed. The historical control data is of limited usefulness in this case because three sets of data (Sprague-Dawley 1974 and 1981 and Long-Evans 1981) all resulted in a positive reponse for the same type of neoplasms.

6. Use of the Sher reference for historical control data.

See comments under #5 above.

7. Discussion of the significance of the neoplasms in the rat testis.

TB acknowledges receipt of the discussions regarding the biological significance of the neoplasms found in the testis of the rats dosed with tetramethrin. Current Agency policy is to regard a positive finding in an oncogenicity study as defining the potential of that chemical to cause or increase the occurrence of neoplasms in test animals. The mechanisms underlying this cause or increase in occurrence is not a primary concern of the Agency for current regulatory purposes. Thus, although the comments provided by the sponsor are of interest, they do not allow the Agency to dismiss a positive oncogenic response for tetramethrin.

TB position as of September 1985

Tetramethrin will be handled in the regulatory process for tolerances and registrations as are all other chemicals which have been shown to be associated with higher incidences of neoplasms.

Attached is a memo addressing the determination of the Q_1^* for tetramethrin as prepared by B. Fisher, statistician TB. Based on the 1974 Sprague-Dawley study, the Q_1^* was determined to be 1.2×10^{-2} $(mg/kg/day)^{-1}$. Review of additional data related to the study used for determining the Q_1^* may result in a change in the above value.

The information regarding exposure (Edwards report June 18, 1984) has been referred back to Registration Division for review by Exposure Assessment Branch.

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List of toxicity studies with technical tetramethrin

The following list of studies are study types which are usually used to build the toxicity data base for a pesticide chemical. Many are known to be available with the technical grade tetramethrin. This list is compiled to assist in the overall review process of tetramethrin.

IMPORTANT NOTE TO PRODUCT MANAGER: Sixteen of the 26 study types listed below must either be submitted to the Agency for review for CORE classification or additional information has been requested as previously indicated in this and other memos. Three study types are indicated as data gaps which should be filled. The product manager is specifically requested to obtain and provide TB with these studies or relevant data for review and to advise the sponsor of the three data gaps as indicated.

Study Type[5]	Status	Must be Submitted[4]
Acute Oral LD_{50}-rat	Coberly-1967[1]	No
Acute Dermal LD_{50}-rabbit	None (Data Gap)	Yes
Acute Dermal LD_{50}-rat	NOT REVIEWED[2]	Yes
Acute Inhalation LC_{50}-rat	Coberly-1967[1]	No
Eye Irritation-rabbits	None (Data Gap)	Yes
Dermal Irritation-rabbits	None (Data Gap)	Yes
Sensitization-guinea pigs	Coberly-1967[1]	No
90 day-feeding-rat	No study	No[3]
180 day-feeding-rat	NOT REVIEWED[2]	Yes
90 day-feeding-dog	Coberly-1967[1]	No
Subchronic inhalation-rat	NOT REVIEWED[2]	Yes
21 day-dermal-	Coberly-1967[1]	No
Teratology-rats	Guidelines-Doherty-1984	No
Teratology-rabbits	Guidelines-Doherty-1984	No
Rabbit Reproduction(?)	Coberly-1967[1]	No
Multigeneration reproduction-rats	Coberly-1967[1]	Yes
Fertility-rats	Supplementary-Doherty-1984	No

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Chronic Feeding/Oncogenicity-rats (two studies)	RESERVED-Doherty-1983, 1984 and 1985 (this memorandum)	Yes
Oncogenicity-mice	Interim report only (Doherty 4/11/83), final report expected in October 1984.	Yes
26 week dog feeding	RESERVED-Doherty-1983, and 1984	Yes
Mutagenicity-DNA damage	NOT REVIEWED[2]	Yes
Mutagenicity-Ames test	NOT REVIEWED[2]	Yes
Mutagenicity-Host mediated assay	NOT REVIEWED[2]	Yes
Metabolism in rats	NOT REVIEWED[2]	Yes
Human Patch Test	Coberly-1967[1]	No
Human exposure	Coberly-1967[1]	No

[1]-These studies are referenced in a review prepared by R. Coberly dated April 27, 1967. No details of the study were provided in Mr. Coberly's review and CORE classification was not assigned.

[2]-This study was referenced in the document entitled "Review of Toxicology on Neo-Pynamin" prepared by the Sumitomo Chemical Co. but TB has no record of a review or of its being submitted to the Agency

[3]-There is no reference to a 90-day rat feeding study which is a usual requirement for a pesticide chemical. Since there is avaliable a 180 day study, a 90 day study need not be conducted and submitted. If there is already a 90 day study available, TB requests that this study be submitted.

[4]-Either the entire study must be submitted or additional specific information must be provided as previously requested.

[5]-It should be noted that depending upon future registrations of tetramethrin additional study types may be required.

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