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

[redacted] 6/19/87

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer-Review on Cypermethrin

FROM: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Addressees

Attached is a package for your review concerning Cypermethrin. This chemical was previously review (May 1, 1986). In order to refresh your memory we are also including a summary and assessment on Cypermethrin contained in the original package.

A meeting to discuss the weight-of-the-evidence on Cypermethrin is scheduled for Wednesday, July 22, 1987, at 10:30 AM in Dr. Farber's office (Rm. 821 CM-2).

Attachment

ADDRESSEES

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin: Peer Review Meeting II.

TOX CHEM No. 271DD

FROM: John Doherty John Doherty April 30, 1987
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Reto Engler
Chief, Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769) 5/1/87

A. Background Information.

In response to the requests made at Peer Review Meeting I for cypermethrin, the following topics have been reevaluated and additional historical control data have been submitted by the ICI Corporation.

1. Discussion of the Maximum Tolerated Dose (MTD) in the rat chronic feeding/oncogenicity study.

2. Discussion of the MTD in the mouse oncogenicity study

3. Neurotoxicity in the multi-generation reproduction study.

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4. Historical control data for the Alderley Park mouse (strain Alpk/AP).

5. Non-neoplastic pathology in mouse lung in the mouse oncogenicity study (Alderley Park strain).

6. Pathological findings in the rat lung in the rat oncogenicity study (Wistar strain).

7. Revised statistical assessment of lung tumor data in the mouse oncogenicity study.

? received only Female data + Hist Controls

Items 1-6 are discussed on the following pages. The report from the statistical work group (item 7) is being prepared separately by the biostatistics team of TB. As of April 29, 1987, this report has not been completed.

B. Summary of information pertinent to the oncogenic classification of cypermethrin.

The following overview should assist the review committee in its classification of cypermethrin.

i. Implicating factors:

Cypermethrin has been demonstrated to statistically significantly increase the frequency of bronchioalveologenic tumors in the lungs of female mice. The increase in frequency of lung tumors occurs at but not in excess of the MTD.

Cypermethrin is structurally related to permethrin which also has been demonstrated to be associated with increased incidences of the same type of lung tumor in female mice.

ii. Mitigating Factors

No other oncogenic response in another organ in female mice, in male mice or in rats has been recognized. The rat studies were determined to have been studied at dose levels which included the MTD.

In the mouse oncogenicity study, the increase in tumors in females occurred at a relatively high dose level (229 mg/kg/day). At lower dose levels which were below the MTD, no increase in lung tumors was noted.

The tumor type (bronchioalveologenic adenoma) is a common tumor type in female mice occurring at a frequency of about 10% in untreated control mice. At the highest test dose level, the increase in tumors presumably caused by cypermethrin was 20% frequency.

Although this type of tumor is common in mice, it is rare in humans.

There was no increase in malignancy (none of the tumors in the high dose group were malignant) or a decrease in latency. There were no test chemical related increases in lesions that were considered possibly pre-neoplastic (such as hyperplasias) or non-neoplastic in the lung.

TB does not consider that cypermethrin has been demonstrated to be mutagenic.

1. Discussion of the Maximum Tolerated Dose (MTD) in the rat chronic feeding/oncogenicity study.

In the rat 90 day subchronic study (ICI Report #CTL/P/327, Jan 1980), rats were dosed with 0, 75, 150 or 1500 ppm of cypermethrin. The test rats in the group receiving 1500 ppm initially showed a slower weight gain and correspondingly less food consumption. After the first three weeks on their test diets, these rats gained weight at the same rate as the controls. The final weights of both the male and female in the high dose groups were depressed.

The liver of the rats dosed with both 150 ppm (males only) and 1500 ppm (males and females) showed proliferation of hepatic smooth endoplasmic reticulum and increased hepatic aminopyrene demethylase activity. These changes were considered by both the testing laboratory and TB to be adaptive responses to cypermethrin and not true toxic responses.

TB considers that the MTD was reached in the highest test dose level in the 1982 rat study (ICI Study #CTL/P/669 June, 1982). In this study, Wistar rats were dosed with either 0,0 (two control groups), 20, 150, or 1500 ppm of cypermethrin (cis/trans ratio of 55:45). The significant effects noted in the high dose test group were decreased body weight gain in males (-12%) and females (-18% to -20%). Body weight depressions in the mid dose group females were 4-5% below control groups.

The high dose test group females had increased liver weight at 52 weeks but not at termination. No other group had increased liver weight. Smooth endoplasmic proliferation was also evident in the high dose group in both sexes which was most evident at 52 weeks but also present at 104 weeks. The mid dose group females were also reported as having a slight increase in smooth endoplasmic reticulum at termination.

The liver of the rats in the high dose group also had elevated levels of aminopyrine-N-demethylase activity at both 52 and 104 weeks. This enzyme was not reported as being elevated in the other test dose groups.

Both the increase in liver weight and aminopyrine-N-demethylase are considered to be adaptive responses to cypermethrin rather than true toxic responses.

No other symptoms of sufficient magnitude were noted to indicate that the high dose was in excess of the MTD. Refer to body weight gain tables attached.

Overall, the depressions in body weight gain noted in this study indicate that cypermethrin was studied at a dose level that was <u>at</u> but not in excess of the MTD.

There were no indications that cypermethrin was related to induction of either neoplastic or non-neoplastic lesions in the lung. Summary tables for the non-neoplastic and neoplastic findings in this study are attached.

2. <u>Discussion of the MTD in the mouse oncogenicity study</u>.

The protocol for the mouse oncogenicity study (ICI Study #CTL/P/687 June, 1982) states that "the dose levels were based on the results of a preliminary 28 day feeding study in the mouse together with our general knowledge of pyrethroid toxicology".

The 28 day preliminary study data were not reviewed by TB. A 28 day preliminary study is considered by TB to be of too short a duration to adequately assess for predicting the MTD. A 90 day study is more suitable.

Thus, the relationship of the highest test dose level to the MTD is best judged by review of the toxicity response noted in the definitive oncogenicity study.

In the definitive study depression in body weight gains were the only outstanding systemic response to cypermethrin noted (except for lung tumors).

Inspection of TABLE 8 (males) and TABLE 9 (females) attached indicates that in males body weight gains were statistically significantly depressed chiefly during the first eleven weeks of the study. The difference reached statistical significance only occasionally afterwards although there was a constant weight difference (decrease) between the high dose group and the controls until termination of the study. During the first 11 weeks depressions in body weight reached -23% (week 1) and to 7 to 10% during weeks 2-11. Afterwards the difference between the controls and the high dose groups was between 5-10% and at weeks 80 to 96 the difference was 12-14%.

Similarly among the females, statistically significant increases were noted most frequently during the first 13 weeks of the study and only occasionally thereafter. At week 1, body weight for the high dose group was -18% below the controls. At other times the body weight was between -3 and up to -16% lower. At 100 weeks (termination) the high dose group was 15% lower than the controls.

The low and mid dose groups were essentially similar to the controls with some occasional and inconsistent differences noted.

In conclusion, the increased incidences in lung tumors in the high dose test groups are thus associated with a dose level that is <u>at</u> but not in excess of the MTD.

3. <u>Neurotoxicity in the multi-generation reproduction study</u>.

There are two multi-generation reproduction studies available. In the first study (Shell Toxicology Laboratory, Study No. TLGR 0188.78, Feb. 1979), cypermethrin was studied at 0, 10, 100, and 500 ppm. No obvious effects indicative of neurotoxicity were reported based on either behavioral responses or the limited amount of histopathology presented.

In the second study (ICI/CTL, Study No. CTL/P/683, 1982) cypermethrin was tested at dose levels of 0, 50, 150 and 750 ppm. The high dose test group was originally started at 1000 ppm, but due to evidence of neurotoxicity (increased sensitivity to sound, ataxia and high stepping gait, and possibly one death), the test level was reduced to 750 ppm. Lowering the dosage level to 750 ppm eliminated the signs of neurotoxicity apparently induced by cypermethrin.

Comments. The observation of neurotoxicity as reported in this study at the dose level of 1000 ppm is not consistent with other studies particularly the rat subchronic and chronic feeding studies. The rat chronic feeding study was started at 1000 ppm but after 3-6 weeks of feeding at this level with only six male rats displaying clinical signs associated with pyrethroid toxicity during the first week of dosing, the dose level was raised to 1500 ppm.

The differences may be in the ratio of cis and trans isomers and in the individual lots used for each study. The cis isomer of cypermethrin and pyrethroids in general is recognized as being more toxic to nerve preparations than the trans isomer. The study reports, however, indicate that the cis/trans ratios and the purity percentages were similar for both the chronic feeding study and the multi-generation study showing the neurotoxicity effects. Since the purity was reported at <95%, there may have been a contaminant present in the lots used for the multi-generation study but not the chronic feeding study.

Both the multi-generation study and the chronic feeding study utilized the same strain of Wistar rat. The strain of rat utilized for the 90 day study was not described as a Wistar but as an Alderley Park strain. Overall species differences would not explain the neurotoxicity.

Lastly, it is possible that the neurotoxicity noted was related to the age of the test animals. Recently presented data (Sheets, Crofton and Reiter, SOT Annual Meeting, 1987) indicate that the type II pyrethroids (to which cypermethrin belongs) are more toxic to younger rats (weanlings) then they are to adult rats.

Overall TB has no satisfactory explanation for the neurotoxicity being noted in the multi-generation reproduction study but not in the chronic feeding/oncogenicity study.

4. Historical control data for the Alderley Park mouse (strain Alpk/AP).

Information on the incidence of potential preneoplastic and neoplastic lesions in the lung for the Alderley Park strain of mouse are attached. The data were derived from seven studies conducted between 1975 and 1985. Five of the mouse studies were by the dietary route. One study each was by the inhalational and by skin painting. The identities of the test chemicals used for these studies were not provided. All of the studies except one were conducted at the ICI Laboratory.

The other study was conducted at Life Science Research facilities (England).

The average frequency (as percent of mice on study, not adjusted for mice at risk) for development of lung tumors in females for the 34 data sets (including mice that were dosed with test chemicals) was determined to be 10.9 +/-6. For females that were in the control groups only, the average was determined to be 10.2 +/-4.9.

In the cypermethrin high dose test group, the corresponding frequency was 20% and the frequencies for the two control, low and mid dose groups were 7.2, 10.0, 8.6 and 11.4 percent. Thus, the high dose group in the cypermethrin study was twice the historical control value.

In only a single study (study B) were the response frequencies in the range of 20% or greater. In study B, the mid dose group had a frequency of 20.3% and the high dose group was 30.5%. Since the control frequencies for this study were 15.3% and 8.5%, the increased frequency in the high dose group suggests a test chemical related effect.

TB concludes that the 20% frequency of lung tumors noted among females in the high dose test group for the cypermethrin study is in excess of the expected range when compared with the historical control data submitted.

5. Non-neoplastic pathology in mouse lung in the mouse oncogenicity study (Alderley Park strain).

The study reports contained tabulated data on non-neoplastic pathology for the terminal kill and one year interim sacrifice mice only (copies of summary tables attached). TB perused the individual animal pathology sheets to assess for the presence of non-neoplastic lesions in the mice which died or were sacrificed moribund during the in-life phase of the study.

Overall there were few incidences of non-neoplastic lesions that were considered to be truly or suggestive of being preneoplastic lesions. The non-neoplastic lung pathology consisted of occasional and sporadic findings of common lesions such as congestion, focal (and otherwise) alveolar macrophage proliferation, pneumonitis, and several other types of singular or infrequent (2-3 occasions) incidences, none of which showed a dose response relationship to the presence of cypermethrin in the diet.

In conclusion, there was no evidence of increases in preneoplastic lesions associated with cypermethrin in the diet.

6. Pathological findings in the rat lung in the rat oncogenicity study.

There were no indications of increased incidences of either neoplastic or nonneoplastic lesions being associated increased levels of cypermethrin in the diet in the rat chronic feeding oncogenicity study (ICI Report #CTL/P/669 June 1982. Refer to copies of the incidence reports attached.

[Note: There were also no indications of test chemical related non-neoplastic or neoplastic lesions in the Shell Research Laboratories Study. The summary tables are not included here because the ICI study was conducted at higher dose levels and included more test animals per dose level and is considered a more definitive study.]

Attachments

1. Body weight gain tables for the rat chronic feeding/ oncogenicity study.
2. Body weight gain tables for the mouse oncogenicity study.
3. Historical control data for the Alderley Park Strain of mouse (ICI submission CTL/P/1614 dated August 19, 1986).
4. Non-neoplastic findings in the mouse oncogenicity study.
5. Summary of neoplastic and non-neoplastic findings in the rat chronic feeding/oncogenicity study.