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

APR 27 1988

006681

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCE

SUBJECT: 10182-REG. Karate 1E Insecticide. Evaluation of Histopathology Slides From Rabbit 21-Day Dermal Study on Cyhalothrin

Tox. Chem. No. 725C - Karate
Related Tox. Chem. No. 271F - Cyhalothrin

TO: George LaRocca, PM #15
Registration Division (TS-767c)

FROM: Pamela M. Hurley Ph.D., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Pamela M. Hurley

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

4/21/88

Background and Request:

A 21-day dermal study was conducted on rabbits with cyhalothrin and was originally submitted with a petition for an Experimental Use Permit for cyhalothrin (53218-EUP-1,2). The Toxicology Branch (TB) reviewed the study and classified it as Core Supplementary because TB believed that the study as presented did not allow TB to determine if certain lesions of the liver and heart were induced by the test material. At that time, TB requested that the Registrant submit slides from the heart and liver for review by our pathologist. The slides were submitted and have subsequently been examined by our pathologist.

It should be noted that in this particular case, cyhalothrin has been accepted as a test representative for both cyhalothrin and PP321 (Karate) (see memorandum from P. Hurley to G. LaRocca, dated 8/27/87). Therefore, this study will be used to satisfy 21-day dermal testing requirements for the technical material for all petitions concerning either cyhalothrin or PP321 (Karate).

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Response:

The Toxicology Branch pathologist has reviewed the histopathology slides submitted by the Registrant and has submitted the following comments (for a complete discussion, see attached memorandum):

1. "The liver lesions are representative of hepatic coccidiosis in rabbits and are not compound-related (i.e., the reaction is not compound-influenced)."

2. "The cardiac lesion is spontaneous in nature and extent and is consistent with laboratory rabbits historical background data."

In addition, the pathologist noted a discrepancy in the clinical chemistry data that most of the rabbits (including controls) had serum protein levels of 6-6.5 gm/100 ml with accompanying albumin serum levels of 5-6 gm/100 ml. He stated that in normal rabbits, the total protein should range between 6-7 gm/100 ml, while albumin should range between 3-3.5 gm/100 ml, or 50-55% of the total serum protein. The alpha, beta and gamma globulins combined should equal the remaining quantity of the total amount of serum total protein.

Conclusions:

The 21-day dermal study is reclassified from Core Supplementary to Core Minimum. However, TB requests that the Registrant submit an explanation for the discrepancy in the clinical chemistry data and/or a statement that the values were similar in historical control animals.

Attachment

cc: L.J. Slaughter

4/20/85

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Results of Histopathologic Evaluation
From Rabbit 21-Day Study on Cyhalothrin
Tox Chem No. 271F Related Tox Chem No. 725C

TO: Pamela M. Hurley, Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Lynnard J. Slaughter, Consulting Pathologist
Toxicology Branch
Hazard Evaluation Division (TS-769) L.J.S.

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Upon your request, I reviewed attachments 1-5, your memorandum, attachment #6 and glass slides of tissue sections of liver and heart that have been stained with hematoxylin and eosin, all of which slides as well as attachments 1-5 were prepared by Imperial Chemical Industries Central Toxicology Laboratories, while attachment #6 was prepared by the Environmental Protection Agency.

Random samples of the slide tissue sections were evaluated histopathologically from certain test and control animals of both sexes.

The following samples of male animal tissues were evaluated:

Vehicle Control	
Test Group 1	Animal #1, path. #00590/81, slide #s 1A,TB,3A & 3B
"	Animal #2, path. #00591/81, slide #s 1A,TB,3A & 3B
"	Animal #3, path. #00592/81, slide #s 1A,TB,3A & 3B
(2 mg/kg)-PEG 300	
Test Group 2 Control 10 mg/kg	Animal #27, path. #00662/81, slide #s 1A,1B,3A & 3B
Test Group 3 100 mg/kg	Animal #45, path. #00603/81, slide #s 1A,1B,3A & 3B
Test Group 4 1000 mg/kg	Animal #61, path. #0064/81, slide #s 1A,1B,3A & 3B

The following samples of female animal tissues were evaluated:

Vehicle Control	
Test Group 1	Animal #11, path. #00737/81, slide #s 1A,TB,3A & 3B
"	Animal #12, path. #00739/81, slide #s 1A,TB,3A & 3B
"	Animal #13, path. #00737/81, slide #s 1A,TB,3A & 3B
(2 mg/kg)-PEG 300	
Test Group 2 10 mg/kg	Animal #34, path. #00745/81, slide #s 1A,1B,3A & 3B
Test Group 3 100 mg/kg	Animal #55, path. #00751/81, slide #s 1A,1B,3A & 3B
Test Group 4 1000 mg/kg	Animal #71, path. #00752/81, slide #s 1A,1B,3A & 3B

Results

Liver

The hepatic-portal inflammatory infiltrates (i.e., plasma cells, lymphocytes and a few heterophils) as well as bile duct proliferation are consistent with those tissue reactions commonly observed in laboratory rabbits with spontaneous low-grade (minimal) coccidiosis infection caused by Emeria stiedae.

These lesions were observed in all treatment groups and control animals. These lesions were not severe or extensive enough to compromise normal liver function, a conclusion supported by the evidence presented in the clinical pathology summary tables. The morbidity and mortality of certain other rabbits narrated in the summary report also strongly suggest that these other rabbits had clinical signs of the enteric form of coccidiosis.

Heart

The heart lesion, fibrosis, represents a healed (advanced) lesion, and only a few early degenerative lesions could be identified in any of these sections of right and left ventricle. The chronic heart lesion (fibrosis) was observed primarily in the interventricular septum left ventricular mass and occasiionally in the musculature of the right ventricle. Also, occasionally focal degenerative lesions (myolysis) were observed in the same sites. These pathologic findings were observed at all dose levels, including the control animals.

This is not an unusual spontaneous lesion to find in the laboratory rabbit. The cause for this lesion is poorly defined. However, several viruses have been incriminated. Also, generalized encephalitozoon infections have been associated with cardiac lesions of this type. In this regard, the summary report on this study describes classic signs of encephalitozoonosis, and it was diagnosed in some rabbits on this study. Therefore, I believe these lesions are spontaneous in nature, are not compound-related and did not compromise the study.

Additional Observation

Finally, the most puzzling summary data were reported in the clinical pathology section. These authors report that most, if not all, test and control rabbits and serum total protein levels of 6-6.5 gm/100 ml, and in these same rabbits albumin serum levels were 6-5 gm/100 ml. I do not understand how this is possible! Moreover, the other hematology and clinical pathology findings do not support such a finding.

Summary Conclusions

1. The liver lesions are representative of hepatic coccidiosis in rabbits and are not compound-related (i.e., the reaction is not compound-influenced).

2. The cardiac lesion is spontaneous in nature and extent and is consistent with laboratory rabbits historical background data.

Recommendation

Reevaluate total protein, albumin and gammaglobulin data to determine if there are typographical errors in the data as provided. If there are no typographical errors, then there are serious implications as to the cause. In normal rabbits, the total protein can range from 6-7 gm/100 ml, while albumin ranges between 3-3.5 gm/100, ml, or 50-55% of the total serum protein. The alpha, beta and gamma globulins combined equal the remaining quantity of the total amount of serum total protein.

ccm #23

Respiratory System (Cont'd)

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Cardiovascular System (Cont'd)

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