



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

AUG 25 1989

007455

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 10182-REG. Cyhalothrin. Addendum to 21-Day Dermal Study

Tox. Chem. No. 271F, 725C
Project No. 9-1313

TO: George LaRocca, PM Team # 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

FROM: Pamela M. Hurley Ph.D., Toxicologist
Section I, Toxicology Branch I
Insecticide, Rodenticide Support
Health Effects Division (H7509c)

Pamela M. Hurley
8/11/89

THRU: Edwin R. Budd, Section Head
Section I, Toxicology Branch I
Insecticide, Rodenticide Support
Health Effects Division (H7509c)

Budd
8/22/89

Record No(s). 243682

Background and Request:

ICI Americas had originally submitted a 21-day dermal study for cyhalothrin on the rabbit in partial fulfillment for the toxicity data requirements for registration of that insecticide. At the time, the Toxicology Branch (TB-I) had some reservations concerning the study and requested submission of slides from specific tissues for examination. The slides were submitted and examined by Health Effect Division's (HED) pathologist, Dr. Lynnard Slaughter. Based upon his conclusions, TB's questions concerning the study were satisfactorily answered. However, Dr. Slaughter raised some questions concerning the clinical chemistry data, particularly relating to the values for the serum protein levels and albumin levels. ICI has responded to Dr. Slaughter's questions and TB has been requested to comment on the response.

Response:

TB received the Registrant's response and submitted it to our pathologist, Dr. Slaughter for review. His comments are provided in the attached memorandum. He believes that the rabbit plasma protein data provided in the 21-day dermal study and in the compiled historical control data from the same laboratory indicate that the test and control rabbits (including the

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historical controls) had severe hypogammaglobulinemia and that the animals were immune-incompetent. He stated that it is not possible to determine whether or not the test chemical would have affected the immune system of the animals under this particular test. TB believes that it is possible that the animals may have been immune-incompetent. Unfortunately, actual measurements of the globulins were not conducted and we do not know what these values were. TB is not requiring a repeat of the 21-day dermal study on the basis of the apparent discrepancies in the plasma protein data for the following reasons:

- 1) There were no significant toxicological effects in the 21-day dermal study.
- 2) Effects on the immune system are not an endpoint which is examined in 21-day dermal studies.
- 3) On the basis of the existing toxicological data on this chemical, any effects on the immune system would not likely affect any toxicological endpoints that may have been observed in this study.

It is noted that in the Registrant's response, it appears that the Registrant is under the impression that the 21-day dermal study is still classified as Core Supplementary. This is not the case. In the memorandum from P. Hurley to G. LaRocca dated 4/27/88, TB stated that based upon our pathologist's review of the slides, the study has been reclassified from Core Supplementary to Core Minimum. The Registrant should be notified of this reclassification.

attachment (1)

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M E M O R A N D U M

TO: Pamela M. Hurley, Ph.D.
Section I, Toxicology Branch I
Insecticide, Rodenticide Support
Health Effects Division (H7509C)

THROUGH: Robert Zendzian, Ph.D.
Section I, Toxicology Branch I
Insecticide, Rodenticide Support
Health Effects Division (H7509C)

FROM: Lynnard J. Slaughter, D.V.M.
Consulting Pathologist
Toxicology Branch
Health Effects Division (H7509C)

DATE: July 24, 1989

SUBJECT: 10182-REO Cyhalothrin/Response to Registrant's
Comments Concerning Rabbit Total Plasma Protein:
Albumin Concentrations

The normal laboratory rabbit has plasma protein concentrations that approximate those depicted in the following table:

TABLE I
Adult Rabbit Plasma Proteins

| | male | | female | |
|------------------|------------|------|------------|------|
| | gm/100 ml | (%) | gm/100 ml | (%) |
| TOTAL PROTEIN | 6.11 + .44 | | 6.14 + .54 | |
| ALBUMIN | 3.6 | (59) | 4.0 | (65) |
| ALPHA 1 GLOBULIN | .55 | (9) | .43 | (7) |
| ALPHA 2 GLOBULIN | .73 | (12) | .50 | (8) |
| GAMMA GLOBULIN | .79 | (13) | .55 | (9) |

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The above table gives the generally accepted protein concentrations for rabbits as reported in the literature. Therefore, the values reported by the registrant for the rabbits utilized on the Cyhalothrin 21-day dermal study and the compiled historical control animal albumin concentrations for other rabbits used on other studies are not representative of the normal laboratory rabbit.

All of the registrant's data indicate that test and control rabbits had severe hypogammaglobulinemia, because 100 percent of their animals' total protein consisted of only albumin. Normally, the combined globulin fractions of the total protein range between 28 to 34 percent, and albumin ranges between 60 to 66 percent of the total protein concentration.

CONCLUSIONS

It appears that the registrant placed immune-incompetent rabbit on this 21-day dermal study. It seems that the vendor and the user of these animals were not aware that the animals used may have been hypogammaglobulinemic, in addition to having hepatic coccidiosis and encephalitozoon infections. Therefore, it is not possible to determine whether or not the test chemical would have affected the immune system of these test rabbits.

RECOMMENDATION

Repeat this study using immune-competent normal New Zealand White Rabbits. You may contact me at your convenience if I can be of further assistance.

SELECTED REFERENCES

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4. Kaneko, JJ and Cornelius, AE (eds). Clinical Biochemistry of Domestic Animals, Vol. 1. New York and London: Academic Press (1970).
5. Kozma, CK, Pelas, A and Salvador, RA. Electrophoretic determination of serum proteins of laboratory animals. JAVMA 151: 865-869 (1967).

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