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

002535

APR 22 1982

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Ms. M. Mautz (16)
Registration Division (TS-767)

SUBJECT: EPA Reg.#100-599, 100-598, PP#8F2057, 9H5231, and FAP 8H5177 - Profenofos (CURACRON) on growing Cotton. CASWELL#266AA
Acc. Nos.: 070513, 245718, 245717, 245716, 245715, 245710, 245709, 245720, 245719, 245721

Petitioner: Ciba-Geigy Corp.
Agricultural Division
Greensboro, North Carolina 27409

Action Requested:

Ciba-Geigy previously submitted mouse carcinogenic and two-year rat chronic feeding studies performed by IBT that subsequently were determined invalid.

The present August 20, 1981, submission contained repeated mouse carcinogenic, a 6-month dog, and two-year rat chronic feeding studies for our review, and also a teratology study for consideration in support of requested tolerances on cotton.

Recommendations by Toxicology Branch:

1. The requested tolerances for use of Curacron on or in cottonseed oil, eggs, meat including poultry, milk and dairy products are not toxicologically supported:

   a. The rabbit teratology study submitted 2/16/82 (Ciba-Geigy #785565) was classified Supplementary Data, and should be repeated. Data reporting was not adequate. The study design was not adequate.

   b. The rat teratology study submitted 2/28/80 (Ciba-Geigy #22741900) contained only summary data. Complete and adequate individual animal data should have been reported. This study was classified as Supplementary Data. Study deficiencies should be resolved, or the study should be repeated.

   c. An acceptable delayed neurotoxicity study should be submitted; however, the results of one neurotoxicity study designated Supplementary Data (#8580-10426) suggested that Curacron does not display delayed neurotoxic potential.

   d. Questions concerning the 3-generation reproduction study must be resolved or the study must be repeated.

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2. If deficiencies relative to the 3-generation reproduction and the rat teratology studies can be resolved, and if the petitioner agrees to submit repeated teratology and neurotoxicity studies within a reasonable length of time, the proposed tolerances can be supported.

3. The 6-month dog study cholinergic NOEL was used to establish an ADI; the dog study ChE effects were more sensitive than similar effects found in the 2-year rat chronic feeding study. A NOEL for the 6-month dog plasma and RBC Cholinesterase inhibition was tentatively determined to be 0.2 ppm (pending clarification of food analysis data). An ADI of 0.0005 mg/kg/day, and a MPI of 0.03 mg/day were established.

The total TMRC (0.0235 mg/day) utilizes 78.35% of the calculated MPI of 0.03 (see attached printout).

4. The results of a calculation to indicate the potential Curacron hazard to infant milk are 3.8 x the ADI. However, RCB memo of 2/14/79 (Donald Reed) shows that no Curacron residues will result from use. Therefore, no hazard to infant milk would result from the proposed use.

5. NOTE: The CSF states that Profenofos technical is 88% pure. Residue Chemistry Branch stated [redacted] Toxicology Branch considers that the toxicity studies designed to evaluate the active ingredient, Profenofos, also evaluated [redacted].

6. New Toxicity Data reviewed in the present report:

a) Teratology, rabbit, HDT = 30 mg/kg. Study is classified as Supplementary Data:

(1) Data reporting was not adequate, and;

(2) The study design was not adequate.

b) Six-month dog - Plasma/RBC ChE NOEL, tentatively 0.2 ppm (LDT). LEL = 2.0 ppm Core-Supplementary Data (pending clarification of feed analysis data).

c) Twenty-four month mouse oncogenicity. No oncogenic potential at levels as high as 100 ppm (HDT). Histopathologic NOEL for male and female mice = 100 ppm (HDT). Core-Minimum Data.

d) Two-year rat chronic feeding. Plasma and RBC ChE NOEL = 0.3 ppm. LEL = 10.0 ppm. Core-Minimum Data

e) An explanation for the extraordinarily high feed analysis data values at the 6th and 7th analyses should be provided (14-18/01/80, and 11-20/02/80). The analysis data for the 0.2 ppm nominal dose rate is critical, since it affects the ChE NOEL. (6 month dog STUDY)

7. A valid 2-generation reproduction study is required.

A 3-generation reproduction study reviewed by Woodrow, 8/9/81 (IBT#623-07944), was later designated an invalid study during an IBT validation review by G. Burin, 4/8/80. This study was revalidated 3/19/82 by G. Burin, following receipt of additional information concerning the study. G. Burin reviewed the validated study 3/25/82 and classified the study as Supplementary Data:

a) The number of histopathological tissues examined could not be determined.

b) Animals selected for histopathology were not randomized.

c) Observations for the F_0 and F_1 generations were not recorded on a daily basis.

d) Animals dying during the study were not adequately examined histologically.

e) Raw data were not adequate: source, strain or age of animals; diet prep. records for weeks 1, 37, and 54; fewer diet analysis results than samples taken.

8. A valid neurotoxicity study is required. Two IBT neurotoxicity studies previously reviewed by Woodrow, 8/19/81, have recently been re-evaluated by the HPB Canadian group under a cooperative IBT validation effort.

a) HPB Canada designated (IBT#8580-11187) an invalid study.

b) IBT test #8580-10426 (Chicken Delayed Neurotoxicity) was designated "valid with reservations." Although there were questions regarding the study design and test compound (the EC formulation was tested), the available raw data did not indicate findings of delayed neurotoxicity.

IBT neurotoxicity study #8580-10426 was designated "valid with reservations" by HPB Canada which is equivalent to EPA's category of Supplementary Data.

b. IBT#8580-11187; Delayed Neurotoxicity. This study was declared invalid by HPB Canada.

c. IBT#8580-10426; Delayed Neurotoxicity. HPB Canada designated this study "valid with reservations". Toxicology Branch classified it as Supplementary Data.

Complete list of Curacron IBT Studies (a copy of this list is to be included in the Caswell file):

1. Technical Chemical, Three-generation reproduction. IBT#623-07924. This study was validated and revalidated, following receipt of additional information concerning the study from Ciba-Geigy, on April 8, 1980, and March 19, 1982, by Gary Burin. Gary Burin reviewed the validated study 3/25/82 and classified the study as Supplementary Data based on the following deficiencies and discrepancies:

a) The number of tissues examined microscopically could not be determined.

b) A bias was introduced into selection of animals for histopathology due to animals being selected in a nonrandom manner.

c) Observations were not recorded on a daily basis for the F_0 and F_1 generations.

d) Animals dying during the course of the study were not examined histologically to the extent required by the protocol.

e) Other deficiencies and discrepancies were concerned with the lack of raw data for environmental conditions, source, strain or age of animals, diet prep. records for weeks 1, 37 and 54 and fewer diet analysis results than samples taken.

2. Formulation, Neurotoxicity - IBT#8580-10426, 2/17/80.

Birds treated with 38% a.i. formulation. Two 21-day successive treatments - doses of 44.5 mg/kg a.i. No neurotoxic signs, or histological evidence of delayed neurotoxicity.

HPB Canada designated this study "valid with reservations". Toxicology Branch classified it Core Supplementary Data.

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3. Technical Chemical. Neurotoxicity - IBT#8580-11187. Invalid (HPB Canada).

4. Technical Chemical. 90-day dog - IBT#611-05912-A. Dog Subacute Oral Feeding "Final Report" - previously reviewed by D. Ritter (2/2/77). No ChE NOEL found. Valid study (HPB Canada). Classification - Core-Minimum Data.

5. Technical Chemical. Rabbit Oral LD_{50} - IBT#601-0481. LD_{50} = > 20, < 200 mg/kg. No validation report. (Artie Williams, SPRD tentatively has no record).

6. Formulation. Rat Oral LD_{50}. IBT#8380-10251. Invalid study (HPB Canada).

7. Formulation. Rat Dermal LD_{50}. IBT#8380-10261. Invalid study (HPB Canada).

8. Formulation. Rabbit Primary Eye Irritation. IBT#8350-10261. P.I. Index = 35.3/110.0. Toxicity Category I. Valid study (HPB Canada). Classification - Core-Minimum Data.

9. Formulation. Rabbit Primary Skin Irritation. IBT#8350-10261. P.I. = 2.4 (moderate irritant). Toxicity Category - III. Valid study (HPB Canada). Classification - Core-Minimum Data.

10. Formulation. Rat Inhalation LC_{50}. IBT#8562-10260. LC_{50} = 11.5 mg/L air. Core Supplementary Data. Valid study (HPB Canada).

11. Formulation. Rabbit dermal LD_{50}. IBT#8350-10564. Invalid Study (HPB Canada).

12. Technical Chemical. Rat subacute oral. IBT#622-05122-B. Valid study (HPB Canada). Classification - Core-Minimum Study.

13. Technical Chemical. Dog 90-Day Feeding. IBT#8531-09996. No ChE NOEL found. HPB Canada validation in progress.

14. Formulation. Mouse Chronic Feeding. IBT#622-07923. No oncogenic potential. No ChE NOEL determined. Supplementary data for feeding study and Core-Minimum for oncogenic. (Validation by G. Burin 5/23/80).

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15. Formulation. IBT No. 622-06895, Rat 2-Year Chronic Feeding. No oncogenic potential. Brain ChE NOEL = 0.08 ppm. LEL = 0.38 ppm. HPB Canada has requested additional information; Validation not complete.

From D. Ritter, TOX profile, 11/1/78. The acute/sensitization data listed below (Ritter TOX profile) is all IBT data (K. Locke, memo of June 14, 1979 - from report of R. Engler, 8/5/77; PP#7G1888) (these data have not been validated).

Acute/Sensitization Toxicity Data

16. Tech. Chemical - Rat LD_{50}, oral = 400 mg/kg BW, Tox. Cat. II,

17. Tech. Chemical - Rabbit LD_{50}, dermal = 472 mg/kg BW, Tox. Cat. II,

18. Tech. Chemical - Rat LC_{50}, inhalation = 2.6 mg/L, Tox. Cat. III,

19. Tech. Chemical - Rabbit Primary Skin Irritation (Draize) = 0.9/8, Tox. Cat. IV

20. Formulation (4 EC) - Rat LD_{50}, oral = 810 mg/kg BW, Tox. Cat. III,

21. Formulation (6E) - Rabbit LD_{50}, dermal = 241 mg/kg BW, Tox. Cat. II,

22. Use dilution - Rabbit LD_{50}, dermal 1:8 and 1:40 = 183 g/kg BW, Tox. Cat. III

23. Formulation (6E) - Rat LC_{50}, inhalation - > 2.45 mg/L, Tox. Cat. IV,

24. Formulation (6E) - Rat primary skin irritation (Draize) = 7.4/8, Tox. Cat. I

25. Formulation (6E) - Rat eye irritation (Draize) = 39/110, Tox. Cat. I,

26. Formulation (6E) - Guinea pig skin sensitivity = negative

Subacute Toxicity

27. Technical Chemical. 90-Day Dog Feeding Study (IBT#611-0592-A). No NOEL determined for RBC ChE at LDT of 2 ppm. Valid Study (HPB Canada). Core-Minimum Data

William S. Woodrow FDC 4/19/82

William S. Woodrow, Ph.D
Toxicology Branch
Hazard Evaluation Division (TS-769)

Diana Kaza DVM. P.H.D.

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