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

003261

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Caswell No. 706A
April 4, 1983

SUBJECT: Propetamphos: Safrotin 2E, PP# 2H 5349 (EPA Registration No. 11273-23).

TO: William Miller (PM-16)
Registration Division (TS-767C)

HISTORY [Sections I through IV of this memo]:

(I) In response to subject petition by Sandoz and submitted studies as support: CBK I.5155/81, Sandoz, Basle, Report #39/81, (dated May 1, 1982), Toxicology Branch concluded (Memo; W. Dykstra to W. Miller, dated August 2, 1982):

[OPEN QUOTES]

"(1) The 3-generation rat reproduction/teratology study is only acceptable as Supplementary Data. Food consumption, body weight and toxic signs data were not reported for maternal and paternal animals. The definitions of fertility index, gestation index, viability index, lactation index I, and lactation index II were not presented in the report. There is no indication of maternal toxicity at 20 ppm in the diet. Maternal toxicity is required for teratogenic evaluation. There is no visceral examination of fetuses in the teratologic portion of the study. The report dose not describe the fetal variations, ossification retardations, and minor and major malformations. A rat teratology study which demonstrates maternal toxicity at the high-dose is required to be submitted.

"(2) The special rat cholinesterase carpet study is required to be submitted.

"(3) The 2-year rat chronic/oncogenic study is only acceptable as Supplementary Data. A summary table of the incidences of non-neoplastic lesions is required to be submitted. Additionally, explanation of the MTD for the study is required.

"(4) The chronic mouse study is considered as Supplementary Data. An explanation of the MTD of the study is required. There is a discrepancy in the report relating to the number of animals surviving the study and the number of animals at termination.

"The survival incidence at termination of the study was summarized as follows:

| Group mg/kg/day | Week 92 Males | Females |
|---|---|---|
| Control I | 14/50 | 24/50 |
| Control II | 31/50 | 28/50 |
| 0.05 | 6/10 | 7/10 |
| 1.0 | 21/50 | 27/50 |
| 6.0 | 28/40 | 23/40 |
| 21.0 | 32/50 | 24/50 |

"The number of animals at terminal kill were:

| Group mg/kg/day | Males | Females |
|---|---|---|
| Control I | 14 | 27 |
| Control II | 31 | 28 |
| 1.0 | 21 | 26 |
| 6.0 | 28 | 23 |
| 21.0 | 29 | 20 " |

[Close quotes].

(II) In a memo to W. Miller in preparation (date, 2/22/83) the Toxicology Branch reviewer (W. Dykstra) drafted the following reviews to further submitted data and the inadequacies noted previously:

[OPEN QUOTES]

"Study 1. Safrotin EC Carpet Study: (A) Cholinesterase Dose/Response. (B) Dislodgeable Residues on Carpets (Sandoz CBK 306B/82026; 8/23/82; Exhibit 2).

"Ten groups of 4 Sprague-Dawley male rats, 180-220 gm per rat, were exposed to carpets consisting of 100% Antron nylon, not 50% wool and 50% acrylic blend. Group assignment and treatment are shown below:

| Non-muzzled | Muzzled | Treatment % a.i. content | Treatment mg/carpet |
|---|---|---|---|
| I | II | 0.0 | 0.0 |
| III | IV | 0.5 | 7.5 |
| V | VI | 1.0 | 15.0 |
| VII | VIII | 5.0 | 75.0 |
| IX | X | 10.0 | 150.0 |

"The carpets were 7 x 12 inches and treated two days prior to exposing the rats and contained non-radioactive and $C^{14}$ propetamphos. Cholinesterase levels of the rats were determined 2 days prior to exposure and after 5 consecutive days of exposure, and at 3 and 6 weeks post exposure.

"Results:

Mean values for cholinesterase levels are presented below which have been taken from the report:

| | Cholinesterase Level/Test Week | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Plasma | | | | RBC | | | |
| Treatment (Group) | -1[a] | 1 | 3 | 6 | -1 | 1 | 3 | 6 |
| Control Non-muzzle (I) | 332 | 336 | 406 | 373 | 143 | 133 | 172 | 128 |
| Muzzle (II) | 378 | 408 | 525 | 452 | 160 | 128 | 169 | 134 |
| Non-muzzle (III) | 359 | 374 | 423 | 365 | 170 | 87[b] | 159 | 127 |
| Muzzle (IV) | 331 | 348 | 402 | 367 | 168 | 132 | 179 | 126 |
| Non-muzzle (V) | 369 | 374 | 429 | 407 | 163 | 119 | 163 | 117 |
| Muzzle (VI) | 324 | 350 | 406 | 374 | 149 | 116 | 160 | 117 |
| Non-muzzle (VII) | 346 | 335 | 408 | 386 | 133 | 150 | 176 | 130 |
| Muzzle (VIII) | 314 | 331 | 425 | 375 | 166 | 123 | 163 | 127 |
| Non-muzzle (IX) | 307 | 295 | 391 | 356 | 172 | 111 | 174 | 131 |
| Muzzle (X) | 381 | 386 | 516 | 454 | 145 | 145 | 179 | 144 |

a/ Pre-test baseline values (all animals non-muzzled)
b/ Statistically different from control. ($P \leq 0.05$).

"The use levels of Safrotin EC are 0.5% and 1.0% a.i. The cholinesterase levels presented, which are 10X the use rate, indicate no substantial cholinesterase depression under the conditions of the study. Other data show dislodgable residues and degradation of propetamphos were not substantial during the study. These data are presented below which have been taken from the study.

| Treatment | | Mcg propetamphos dislodged/Exposure | | | | | |
|---|---|---|---|---|---|---|---|
| Mg ai | % Conc. ai | 1 | 2 | 3 | 4 | 5 | 5a |
| 6.5 | 0.5 | 0.24 | 0.03 | 0.00 | 0.00 | 0.00 | 0.07 |
| 13.0 | 1.0 | 1.50 | 0.38 | 0.26 | 0.20 | 0.19 | 0.31 |
| 62.0 | 5.0 | 14.0 | 4.8 | 3.7 | 3.1 | 3.2 | 5.6 |
| 132.0 | 10.0 | 29.5 | 10.0 | 8.1 | 7.4 | 7.0 | 16.1 |

| Treatment: | % ai Conc. | 0.5 | 1.0 | 5.0 | 10.0 |
|---|---|---|---|---|---|
| | mg/carpet | 6.5 | 13 | 62 | 132 |

| Dislodgeables: | % Dose | 0.001 | 0.002 | 0.009 | 0.012 |
|---|---|---|---|---|---|
| | Mcg/Sample | 0.07 | 0.31 | 5.6 | 16.1 |

"[Reviewer's] Conclusions: The data presented support the conclusion that exposure to Safrotin EC (propetamphos) as demonstrated in the study is not a significant hazard to exposed persons from this use pattern.

"Study 2. Summary Incidence Table of Non-neoplastic findings in the chronic/oncogenic rat feeding study (Exhibit 3)

"No treatment-related findings were present in the non-neoplastic summary incidence tables." [Reviewer's] Conclusion: The NOEL is 12.0 ppm. Classification: Core Minimum Data.

"Study 3. MTD Evaluation for Propetamphos-2 year chronic/oncogenic rat feeding study (Exhibit 4).

The submitted data indicate that the highest dose of 120 ppm can be considered the MTD for the study. Mean body weight gain of males and females of the high-dose group were significantly decreased in comparison to the controls and other groups up to week 67 for males and up to week 82 for females.

"Study 4. Mouse chronic/oncogenic feeding study (Exhibit 5); a. The discrepancy in the number of surviving mice and an explanation of the MTD:

The table below, taken from the report, shows the differences in surviving mice.

WIL RESEARCH LAB'S REPORT:

| Control I Female | Low 1 mg/kg/day Female | Mid 21 mg/kg/day Female | High 21 mg/kg/day Female |
|---|---|---|---|
| 24/50 | 27/50 | 24/50 | 32/50 |
| SANDOZ STATISTICAL REPORT: | | | |
| 27/50 | 27/50 | 20/50 | 29/50 |
| CONSULTANT'S PATHOLGOY REPORT (Dr. BARTHEL): | | | |
| 27/50 | 26/50 | 20/50 | 29/50 |

"The discrepancy in the number of surviving mice is adequately presented in the Sandoz report. Having checked Sandoz, Inc.'s raw data and processing forms and having had WIL Research Lab recheck their data, WIL has indicated as of October 26, 1982 that the numbers underlined in the above table are incorrect. Their recount totals are now the same as the Sandoz Statistical Report and the Consultant's Pathology Report."

Additionally, the MTD level for the study was based on reduced bodyweight gain at 42 mg/kg/day in a subacute study and previously agreed to on 12/28/78 by Toxicology Branch. Classification: Core-Minimum Data.

William Dykstra Charles Smallwood for CSC 9/24/83

William Dykstra, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769C)

[Close Quotes]

(III). On November 4, 1982, Sandoz, Inc. Corp Protection (San Diego, CA) submitted a two-generation study in rats (reported in three separate segments), performed in Japan by Sandoz Pharmaceutical Ltd., Tokyo, as teratogenicity and reproductive tests (Report No. CBK I. 4830/80, May 16, 1980) in support of their food additive tolerance petition, 2H-5349. [As stated in the Introduction of the submission, it was noted that this study was conducted in Japan for the purpose of obtaining a Japanese registration, since that country only considers registrations that are supported in part by toxicology data generated in Japan.].

Toxicology Branch review of this study judged this Japanese study as SUPPLEMENTARY DATA, due to the following deficiencies [Memo: I. Mauer to W.H. Miller, dated January 28, 1983]:

[OPEN QUOTES]

"(1) Different groups of animals were used for the three segments, and no group was treated through two generations.

"(2) An LEL for any clinical changes was not detemrined (HDT = 2 mg/kg, stated to decrease plasma cholinesterase), and no clinically observable effects were found at the highest dose.

"(3) No measurements of cholinesterase were made in test animals; neither a NOEL or LEL (with or without clinical effects) was determined.

"(4) Identity and concentrations of impurities in the test substance (technical) were not provided; purity of the technical was stated as 92%.

"(5) Females of the $P_1$ generation received test substance for only 2 weeks before and during mating (an 8-week pre-mating treatment period is recommend in both sexes).

"(6) $F_1$ animals were not observed to weaning.

"(7) $F_2$ animals were not observed to weaning.

"(8) Gross necropsies were not performed on the $F_2$.

"[The second segment, Study B of the submitted study might have been acceptable as a teratogenicity assay with postnatal segment with the demonstration of observable maternal clinical effects, and a NOEL for fetal effects in the absence of maternal clinical effects.]"

[CLOSE QUOTES].

A detailed evaluation of the study followed this summary (part of the January 28, 1983 memo).

(IV) In further response, March 7, 1983, Sandoz re-submitted Studies CBK I. 5155/81 (Basle rat reproduction study) and CBK I. 4830/80 (Japanese rat reproduction study), as well as an itemized rebuttal (quoted here in its entirety) to the issues raised by Tox. Branch in evaluating these studies:

[OPEN QUOTES]

"INTRODUCTION

"On May 1, 1982, a propetamphos food additive tolerance petition was presented to the Agency. Included therein were the results of a rat reproduction teratology study entitled "Propetamphos 3-Generation Study in Rats" (Agro Dok CBK I.5155/81). The Agency's comments relative to this study (hereafter referred to as the Basel study), were forwarded to Sandoz in correspondence of Agust 9, 1982 from Mr. W. Miller. In response, Sandoz presented a second such study which was conducted by Sandoz in Japan entitled "Propetamphos Reproduction Study in Rats" (Agro Dok CBK I.4830/80) on November 4, 1982 (hereafter referred to as the Japanese study). By copy of an internal memo dated January 28, 1983 from Dr. Irving Mauer of the Hazard Evaluation Division/OPP to Mr. W. Miller of the Registration Division, OPP, comments relative to this second study were forwarded to Sandoz.

"We believe that the questions raised in the above referenced Agency correspondence are addressed in their entirety by the data presented in the Japanese study which was primarily designed to be a teratology study and a rewrite of the Basle study included here for review. The 1339 page rewrite was done from the raw data to improve the completeness and clarity of the original report.

Itemized below are the questions raised by the Agency and where in the studies they are answered. The reviewer is cautioned to note that the Basel study page references given below refer to the rewritten report included in this submission.

"1. Maternal toxicity in rat teratology study

A. Japanese Study Part B, page A-2

Doses were set by pretest toxicity results. High dose was 2 mg/kg/day because pretest showed a 21% decrease in CHE at 1 mg/kg/day for two weeks and 40% at 3 mg/kg/day. Significant decreases in liver weight (P=.01) were seen in male and female parents.

B. Basel Study

Maternal and paternal toxicity is summarized on pages 9, 10 and 12. Significant clinical chemistry alternations were demonstrated in the parents of animals investigated for teratological parameters.

"2. Visceral examination of fetuses in the teratology portion

A. Part B of the Japanese Study contain complete visceral examinations, pages 70-72.

B. Visceral examinations were made in the Basel study and are reported on pages 99-103 for the F1B, F2B and F3B generations.

"3. Fetal variations, ossification retardations, and minor and major malformations

A. The Japanese study Part B contains these elements on pages 71-72.

B. The Basel study contains these elements on pages 99-103.

"4. Definitions of fertility index, gestation index, viability index, lactation index I and II of the Basel study are now included on page 4.

"5. Technical propetamphos from Batch P 16/77 was utilized in both of the studies discussed above. The impurities of this batch are within the limits of those reported in Study CBK 4641/82. A copy of this report follows the tab marked "Analytics".

"For the reviewer's convenience, a copy of the Agency's comments received to date with regard to this issue follow this introduction."

[CLOSE QUOTES]

It is to this rebuttal that the present memo is addressed (point-for-point):

ISSUE ITEM 1. Maternal toxicity in rat teratology study.

Registrant Rebuttal:

[OPEN QUOTES]

"A. Japanese Study Part B, page A-2

Doses were set by pretest toxicity results. High dose was 2 mg/kg/day because pretest showed a 21% decrease in CHE at 1 mg/kg/day for two weeks and 40% at 3 mg/kg/day. Significant decreases in liver weight (P=.01) were seen in male and female parents.

"B. Basel Study

Maternal and paternal toxicity is summarized on pages 9, 10 and 12. Significant clinical chemistry alternations were demonstrated in the parents of animals investigated for teratological parameters."

[CLOSE QUOTES]

Agency Response:

A. Japanese Study - Nowhere in the study reviewed by TB ("the Japanese study") are "...significant decreases in liver weight (P = .01) ....in male and female parents..." mentioned and no tabular (any other form of) data (by summary or individual animal organ weight) were included in the submission copy reviewed. The Agency would need to see the raw data for these liver weight effects the in main study.

In domestic animals and pets, the Agency may use (internally) a rough guide to cholinesterase inhibition known a the "5X rule," e.g., a level 5X label recommendation not producing adverse effects which might produce slight (clinical) effects; for plasma cholinesterase, this would be approximately 40% average inhibition. However, no clinical consequencies were reported (or even mentioned) in the submitted Japanese study, as reviewed. Further, for lab. animals, some ponderal and/or other clinical toxicity must be demonstrated at the HDT for the study in order for that study to be considered minimal data.

Finally, acute oral $LD_{50}$ data in this strain of rats would also be useful, if available.

Hence, the Japanese study remains SUPPLEMENTARY DATA, both in its entirety, and for its several reproduction/ teratology segments.

B. Basel Study

Pages 9, 10 and 12 of the Basle study summarize clinical chemistry values (ChE inhibition) for the $F_1$ generation (not the parental animals) at the HDT (20 ppm, average

intake = 1.74 for males, and 2.01 mg/kg for females over 13 weeks treatment --- from p. 160 of report) which did not reach 40%, coincident with reporting increased relative (but not absolute) weight for male liver, testes and brain, as well as increased kidney weights of treated females (both reported on p. 10); contrasted with reduced (?) absolute (but not relative) weight for high-dose males (reported on p. 12)! Other variations in clinical chemistry values were considered by the authors as "...not related to treatment...."

ISSUE ITEM 2. Visceral examination of fetuses in the teratology portion.

Registrant's Rebuttal:"

[OPEN QUOTES]

"A. Part B of the Japanese Study contain complete visceral examinations, pages 70-72.

"B. Visceral examinations were made in the Basel study and are reported on pages 99-103 for the F1B, F2B and F3B generations."

[CLOSE QUOTES]

Agency Response:

A. Japanese Study: Pages 70-72 of the report does indeed: "...contain complete visceral examinations..." of ($F_1$) fetuses, which indicate decreases in dumbbell-shaped vertebral bodies at all doses (i.e., apparently no NOEL).

Further, as indicated in the Agency review of January 28, 1983, study Summary Tables B-15 and B-16 recorded further significant skeletal and ponderal (organ weight) changes in $F_1$ animals.

Finally, no maternal toxicity was reported at the HDT.

Hence this (teratology) segment remain SUPPLEMENTARY DATA due to the deficiencies noted in the TB evaluation.

B. Basle Study: Visceral data are reported on pp. 99-103 for the F1B, F2B and F3B generations (as registrant notes).

ISSUE ITEM 3. Fetal variations, ossification retardations, and minor and major malformations.

Registrant's Rebuttal:

[OPEN QUOTES]

"A. The Japanese study Part B contains these elements on pages 71-72.

"B. The Basel study contains these elements on pages 99-103."

[CLOSE QUOTES]

Agency Response:

A. Japanese Study: [See Agency Response for ISSUE ITEM 2, above].

B. Basle Study: [See Agency Response for ISSUE ITEM 3, above].

[OPEN QUOTES]

ISSUE/ITEM 4. "Definitions of fertility index, gestation index, viability index, lactation index I and II of the Basel study are now included on page 4."

[CLOSE QUOTES]

Agency Response: Noted; deficiency is fulfilled.

ISSUE ITEM 5. (Registrant's Rebuttal): [OPEN QUOTES]

"Technical propetamphos from Batch P 16/77 was utilized in both of the studies discussed above. The impurities of this batch are within the limits of those reported in Study CBK 4641/82. A copy of this report follows the tab marked 'Analytics'".

[CLOSE QUOTES]

Agency Response: Noted and acceptable to TB (i.e., deficiency would be fulfilled), if Residue Chemistry Branch concurs.

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Irving Mauer, Geneticist
Toxicology Branch/HED (TS-769c)

4-18-83

04/07/83