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

OCT 6 1983

MEMORANDUM

Casewell No. 706A

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769) WLB 10.4.83

SUBJECT: Propetamphos Food Additive Petition (2H5349): Rebuttal letter, Sandoz to US EPA, (dated) August 17, 1983, EPA Accession No.: 251002

This is in response to the registrant's rebuttal (8/17/83) with respect to the evaluation of both the Basel and Japanese reproduction studies, Core graded as Supplementary Data, (Memo's: January 28, 1983, and April 7, 1983). Six exhibits were enclosed under this rebuttal:

Exhibit 1: "Raw data of a pilot study on Cholinesterase-Determination", by K. Futakuchi, Sandoz Pharmaceuticals, LTD, Tokyo.

Exhibit 2: "Raw Organ Weights of F_1 Parents"

Exhibit 3: "Acute Tox Study in Rats and Mice with PROPETAMPHOS"

Exhibit 4: "PROPETAMPHOS 3-Generation Rat Study" (Tabular data), as follows:

(1) "Cholinesterase Inhibition with mean High Dose Values given as % of Control at indicated Time in Weeks"

(2) "Glucose Increase with mean High Dose Values given as % of Control at indicated Time in Weeks"

(3) "Cholesterol Effect with mean High Dose Values given as % Control at indicated Time in Weeks"

Exhibit 5: "PROPETAMPHOS 2-Year Rat Feeding" (Tabular data), as follows:

(1) "Cholinesterase Inhibition with Low and Mid Dose[1]. Values given as % Control"

"PROPETAMPHOS 90-Days Rat Study

(2) "Cholinesterase Inhibition with High Dose. Values[2] given as % Control"

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6 pages

Exhibit 6: "Drug Intake Values for all Dosages During a 13-Week Feeding Period"

This memo responds only to the rebuttal regarding the Japanese study.

In the August 17, 1983 rebuttal, Sandoz takes issue with the Agency's Core Classification (deficiencies) on two points: "(i) there were insufficient decreases in cholinesterase levels, and ii) data to support the registrant's claim of effect on liver weight were not provided". Registrant submitted two exhibits to support this rebuttal: viz "Exhibit-1," cholinesterase data from the Pre-Test previously referred to (final report on The Japanese study); and "Exhibit-2," the raw organ weight data from that study (said to have been omitted from that final study report).

Sandoz further contends: (i) "..... that the arbitrary requirement to show an average cholinesterase inhibition of 40% is unreasonable. The "Pretest" data show a clear enzyme inhibition at 2 mg/kg/day in the same strain of rats used in the Japanese teratology study"; and (ii) "..... that there is a treatment-related lowering of liver weights of the F_1 rats in the Japanese study. It is possible that this reflects an in utero effect that occurred when the F_0 parents were treated with the test compound. As requested, we are including the raw organ weight data from the F_1 parents of the Japanese study."

The registrant also disagrees with the Agency regarding the lack of a NOEL: " ..... because of the data on dumbbell-shaped vertebrae bodies. The correct interpretation of these data is that they indicate that a delay in ossification in the controls compared with the treated groups. Due to wide variations in this observation, this difference is most likely not a true difference between groups. Our Japanese colleagues have informed us that based on 1466 control fetuses the incidence in their laboratories is 9.08% with a range of -14.48 to +32.65%."

Sandoz also provided acute oral LD_{50} data on this strain of rats (Exhibit #3 of this rebuttal submission).

Finally, Sandoz disagrees with the Agency's classification of the teratology segment(s) of the Japanese study as SUPPLEMENTARY DATA.

The Agency's response to these rebuttals (point-for-point) follows:

(1) Registrant Rebuttal, (i) and (ii) - August 17, 1983

"JAPANESE STUDY

"It is our understanding that the Agency considers the Japanese teratology study deficient on two accounts; i) there were insufficient decreases in cholinesterase levels, and ii) data to support the registrants claim of effect on liver weight were not provided. Enclosed for Agency review are: Exhibit-1 cholinesterase data from the "Pretest" referred to in the final study report on the Japanese teratology study and Exhibit-2 the raw organ weight data from the study that was not in the final study report.

"Sandoz contends that the arbitrary requirement to show an average cholinesterase inhibition of 40% is unreasonable. The "Pretest" data show a clear enzyme inhibition at 2 mg/kg/day in the same strain of rats used in the Japanese teratology study.

"Sandoz further contends that there is a treatment-related lowering of liver weights in the F_1 rats in the Japanese study. It is possible that this reflects an in utero effect that occurred when the F_0 parents were treated with the test compound. As requested, we are including the raw organ weight data from the F_1 parents of the Japanese study."

Agency Response: If the "Pre[illegible] cholinesterase data ("Exhibit-1") are the same as previously submitted (as suggested by registrant), these data have already been reviewed, and accepted. However the typed tabulation: "Effect of Propetamphos on blood cholinesterase activity in rats" of Exhibit 1 indicates a "clear enzyme reduction" at 3 mg/kg (not the 2 mg/kg dose stated in the rebuttal; apparently there was no test at 2 mg/kg. [This reviewer cannot interpret the following two tabulations of Exhibit 1," except that they may represent the raw data sheets for the typed summary.] Thus it does not seem "unreasonable" that some consistent effect, clinical or chemical, be demonstrated at the highest dose tested (2 mg/kg). This was not done.

Exhibit 2 of this rebuttal ("Raw Organ Weights of F_1 Parents") appears to be xerox copies of raw data sheets from "SEGMENT II F_1" animals; but no summary tabulations accompany these raw data sheets, and they are not in a form that can be reviewed. The Agency accepts these raw data without comment, but considers the registrant's "explanation" moot.

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(2) Registrant Rebuttal:

"We disagree with the Agency that there is no NOEL because of the data on dumbbell-shaped vetebrae bodies. The correct interpretation of these data is that they indicate that a delay in ossification in the controls compared with the treated groups. Due to wide variations in this observation, this difference is most likely not a true difference between groups. Our Japaneses colleagues have informed us that based on 1466 control fetuses the incidence in their laboratories is 9.08% with a range of -14.48 to +32.65%."

Agency Response: The logic of this rebuttal is internally inconsistent as well as contradictory. Controls would not show "delay in ossification," rather there might be an acceleration of ossification in treated animals - if there were a "true difference between groups." However, the Agency accepts the wide variation in control "dumbbell-shaped vertebrae bodies," as reported by the Japanese investigators, and thus no issue relative to a NOEL exist for this attribute.

(3) Registrant's Rebuttal:

"The Agency indicated that it would be helpful to have acute oral LD_{50} data on the strain of rats used in this study. This information is presented as Exhibit #3."

Agency Response: The Agency accepts these additional data without comment. We note, however, the following:

(i) Acute oral LD_{50} data submitted were determined with propetamphos dissolved in corn oil, whereas the reproduction/teratology studies were carried out with an olive oil preparation.

(ii) Propetamphos in corn oil appears to be more toxic by gavage than by parenteral (subcutaneous) administration.

(4) Registrant's Rebuttal:

"Finally, regarding the Japanese study, the Agency reviewer suggested that "Summary Tables B-15 and B-16 recorded further skeletal and ponderal changes in the F_1, animals". As we have mentioned above, the liver weights for males and females were significantly reduced at the high dose only. All other significant findings were not dose response related and consistent for both sexes."

Agency Response: The Agency accepts these statements, but as suggested above, considers the differences in liver weights not of biological significance and hence not a true "effect" (level).

(5) Registrant's Rebuttal:

"Based on the above we cannot agree with the Agency that the teratology segments of the Japanese study, should be classified SUPPLEMENTARY DATA."

Agency Response: The "teratology segments" of the Japanese submission (referred to as "Test B" in the Final Report and Agency reviews) does not qualify as a comprehensive teratogenicity study, (and hence was Core Classified as SUPPLEMENTARY DATA), since: (i) No observable maternal clinical effects were noted in dams treated at the HDT (as so stated by the investigators themselves); and (ii) apparently there is no effect level for any frank fetal effect, either in the presence or absence of maternal effects.

Finally, the Agency classified the entire three-part Japanese study, as well as each one of its parts, as CORE SUPPLEMENTARY DATA for the following major deficiencies, as an inadequate evaluation of the compound according to FIFRA Guidelines and good laboratory practice for studies of this type:

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

(2) No clinically observable effects were found at the highest dose.

(3) 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 recommended in both sexes).

(4) F_1 animals were not dosed in any segment of these studies.

(5) F_2 animals were not observed to weaning.

(6) Gross necropsies were not performed on the F_2.

These deficiencies were not addressed in the registrant's rebuttal of August 17, 1983.

Irving Mauer, Geneticist 09-28-83
Toxicology Branch/HED (TS-769)

ADDENDUM:

Exhibits 4, 5, and 6 are not addressed in this response, since they do not refer to the Japanese reproduction study.