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CASWELL FILE

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

008885

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propetamphos; ID# 113601-002724; 6(a)(2) data; 83-5; Combined Chronic Toxicity/Carcinogenicity Study in Rats; MRID# 164890

| | |
|---|---|
| Caswell No.: | 706A |
| Project No.: | 2-0113 |
| Rereg. Case No.: | 2550 |
| Submission No.: | S382946 |
| MRID No.: | 164890 |

TO: Christine Rice, PM Team #52
Reregistration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D. William Dykstra 11/21/91
Review Section I, TB-I, IRS
Health Effects Division (H7509C)

THRU: Roger Gardner, Section Head Roger Gardner
Review Section I, TB-I, IRS
Health Effects Division (H7509C) 11-22-91

Requested Action: Review combined chronic toxicity/carcinogenicity study submitted as 6(a)(2) data.

Conclusion and Recommendation:

The study is only acceptable as Core-Supplementary data and does not support reregistration. Quality assurance was not performed, raw data for toxic signs were not reported, and dietary analyses data were not presented.

The carcinogenic potential was negative up to 120 ppm which was the MTD for the study.

At 120 ppm, there were consistent decreases in body weight gain, increases in toxic signs, decreases in RBC and brain ChE in both sexes, increased incidence of focal atrophy of exocrine cells in the pancreas, and increased incidence in both sexes of lymphoreticular proliferation in the lungs.

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At 12.0 ppm there were decreases in plasma ChE in both sexes and increased incidence in females of focal atrophy of exocrine cells in the pancreas.

The NOEL for the study is 6.0 ppm for ChE inhibition and for systemic toxicity.

Based on the NOEL of 6.0 ppm (0.3 mg/kg/day) in this study and using a 100-fold uncertainty factor, the RfD would be 0.003 mg/kg/day which is <u>less</u> than the current RfD of 0.005 mg/kg/day (mouse study). Therefore, a new RfD should be determined. Additionally, the study results cited by the registrant (toxic signs) do not meet the 40 CFR 158.34 flagging criteria for adverse effects.

A DER is attached.

Attachments

PROPET.WD/LCA

Reviewed by: William Dykstra, Ph.D. William Dykstra 11/21/91
Review Section I, Toxicology Branch I (H7509C)
Secondary Reviewer: Roger Gardner, Section Head Roger Gardner 11-22-91
Review Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

Study Type: 83-5; Combined Chronic Toxicity/Carcinogenicity - Rats

TOX Chem No. 706A
MRID No.: 164890

Accession Number: N/A

Test Material: Propetamphos technical, 91.8% purity

Synonyms: Safrotin EC

Study Numbers: AGRO, DOK, CBKI 5214/81

Sponsor: Sandoz, Inc.

Testing Facility: University of Berne; Inst. of Pathology

Title of Report: 2-Year Chronic Feeding Study in Rats

Author: Dr. H. Luginbuhl

Report Issued: June 22, 1981

Conclusion: The carcinogenic potential was negative up to 120 ppm (HDT) which was the MTD. At 120 ppm, there were consistent decreases in body weight gain, increases in toxic sign, decreases in RBC and Brain ChE in both sexes, increased incidence in females of atrophy of pancreatic exocrine cells, and increased incidence in both sexes of lymphoreticulor proliferation of the lungs. At 12.0 ppm, there were decreases in plasma RBC in both sexes and increased incidence of focal atrophy of exocrine cells of the pancreas in females. The NOEL's in the study are 6.0 ppm for ChE inhibition and for systemic toxicity.

Classification: core-supplementary

(a) No dietary analyses reported
(b) No quality assurance or GLP statements were reported.
(c) Raw data for toxic signs not reported

Special Review Criteria (40 CFR 154.7) N/A

A. MATERIALS:

1. Test compound: propetamphos, tech., Description - brownish liquid, Batch # - 4552, Purity - 91.8%, contaminants: list in CBI appendix.

2. Test animals: Species: Rat, Strain: OFA (Sprague-Dawley), Age: 3-4 weeks, Weight: males, 64gm; females, 60gm, Source: Sandoz Breeding Center at Basie.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

| Test Group | Dose in diet (ppm) | Main Study 24 months male | Main Study 24 months female | Interim Sac. 0 months male | Interim Sac. 0 months female |
|---|---|---|---|---|---|
| 1 Cont | 0 | 55 | 55 | | |
| 2 Low (LDT) | 6 | 55 | 55 | | |
| 3 Mid (MDT) | 12 | 55 | 55 | | |
| 4 High (HDT) | 120 | 55 | 55 | | |

2. Diet preparation

Diet was prepared weekly and stored at room temperature. Samples of treated food were analyzed for stability and concentration at beginning and quarterly.

Results - Dietary analyses results were not provided in the report.

3. Animals received food (859/860 G4), In powdered diet (sieve 30/45) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: parametric and non-parametric at $P<0.05$.

5. A signed quality assurance statement was not stated as having been performed. Additionally, there were no GLP statements reported.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality.

Toxicity: Although raw data were not provided, the report states that beginning in week 34, one male and 16 females at the high-dose showed red belly marks and hair loss on the belly and between the hindlegs. The animals with these signs were weak and limp. The remainder of high-dose rats showed slight hyperflexia. The NOEL for toxic signs is 12.0 ppm. These toxic signs were the registrant's stated evidence for 6(a)(2) data.

Results -

Mortality - the following mortality occurred during the study. Males were sacrificed at week 90 and females at week 108.

| Dose (ppm) | Males | Females |
|---|---|---|
| 0 | 43/55 | 35/55 |
| 6 | 37/55 | 36/55 |
| 12 | 41/55 | 37/55 |
| 120 | 15/55 | 18/55 |

2. Body weight

Animals were weighed weekly for 56 weeks, then for every two weeks for remainder of the study.

Results - High-dose males showed a highly significant decrease in body weight gain up to week 67 (6-14%). High-dose females showed a highly significant decrease in body weight gain up to week 82 (12-14%). At week 13, the decrease in body weight gain was 6% for males and 12% for females. The NOEL for body weight gain is 12.0 ppm for both sexes.

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results - Food consumption: Food consumption was comparable between controls and each treated groups of both sexes during the study. The NOEL is 120 ppm (HDT).

Compound Intake: In mg/kg/day estimates, compound intake was as follows:

| Dose (ppm) | Males | Females |
|---|---|---|
| 0 | --- | --- |
| 6 | 0.376 | 0.412 |
| 12 | 0.632 | 0.689 |
| 120 | 5.891 | 7.602 |

4. Ophthalmological examination were not performed

5. Blood was collected before treatment and at 4, 8, 13, 27, 52, 78, 91 (males), 104, 109 (females only) weeks for hematology and clinical analysis from 8/sex/groups. The CHECKED (X) parameters were examined.

a. Hematology

| X | | X | |
|---|---|---|---|
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Mean corpuscular HGB (MCH) |
| X | Leukocyte count (WBC)* | X | Mean corpusc. HGB conc.(MCHC) |
| X | Erythrocyte count (RBC)* | X | Mean corpusc. volume (MCV) |
| X | Platelet count* | | Reticulocyte count |

* Required for subchronic and chronic studies

Results -

Males: No consistent, time-related or dose related effects were observed. Occasional single deviations were observed in treated rats in comparison to controls, but no trends were evident.

Females: No consistent time-related or dose-related effects were observed. Occasional single deviations were observed n treated groups in comparison to controls, but no trends were evident.

NOEL for hematological findings is 120 ppm (HDT).

b. Clinical Chemistry

| X | Electrolytes: | X | Other: |
|---|---|---|---|
| X | Calcium* | X | Albumin* |
| X | Chloride* | X | Blood creatinine* |
| | Magnesium* | X | Blood urea nitrogen* |
| | Phosphorous* | X | Cholesterol* |
| X | Potassium* | | Globulins |
| | Sodium* | X | Glucose* |
| | Enzymes | X | Total bilirubin |
| X | Alkaline phosphatase (ALK) | X | Total serum Protein (TP)* |
| X | Cholinesterase (ChE)# | | Triglycerides |
| | Creatinine phosphokinase*^ | | |
| X | Lactic acid dehydrogenase (LAD) | | |
| X | Serum alanine aminotransferase (also SGPT)* | | |
| X | Serum aspartate aminotransferase (also SGOT)* | | |

* Required for subchronic and chronic studies
# Should be required for OP
^ Not required for subchronic studies

Results -

Males: In the second year, BUN values in all male treated group (though less in high-dose males) were increased beyond the normal control values. Creatinine was elevated in mid-dose males (week 52) and in all treated and control groups in week 78 and 91. These findings were not considered compound-related since they were sporadic, not dose-related, and included controls at weeks 78 and 91.

Females: No consistent, time-related or dose-related effects were observed in treated female groups in comparison to controls.

The NOEL is 120 ppm (HDT) for Clinical pathology.

Cholinesterase Activity: A variation of ± 20 to 25% of control values is considered normal by the laboratory. No significant decrease in plasma or RBC cholinesterase inhibition was present in low-dose (6 ppm) rats as shown below:

CHOLINESTERASE ACTIVITY (% deviation vs. control)

Plasma-ChE

| Group/Month Male (ppm) | 1 | 2 | 3 | 6 | 12 | 18 | 21 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|
| 6 | +1 | +3 | -9 | -13 | +1 | -18 | -2 | | |
| 12 | -3 | +6 | -14 | -15 | -4 | -29 | -2 | | |
| 120 | -30 | -18 | -33 | -41 | -23 | -55 | -49 | | |
| Female (ppm) | | | | | | | | | |
| 6 | +8 | -3 | -9 | -17 | -14 | -6 | | -18 | +8 |
| 12 | -4 | -2 | -17 | -23 | -7 | -11 | | -32 | -23 |
| 120 | -42 | -55 | -63 | -63 | -66 | -55 | | -68 | -52 |

RBC-ChE

| Group/Month Male (ppm) | 1 | 2 | 3 | 6 | 12 | 18 | 21 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|
| 6 | -4 | -4 | -2 | -11 | -8 | -4 | -13 | | |
| 12 | -14 | -20 | -17 | -21 | -9 | -12 | -14 | | |
| 120 | -37 | -42 | -46 | -48 | -25 | -37 | -39 | | |
| Female (ppm) | | | | | | | | | |
| 6 | -5 | -6 | -7 | -11 | -12 | -7 | | -9 | -9 |
| 12 | -16 | -16 | -17 | -21 | -18 | -13 | | -12 | -14 |
| 120 | -42 | -41 | -41 | -41 | -41 | -35 | | -37 | -32 |

A moderate inhibition (-34 to -40%) of brain cholinesterase was noted in the high-dose rats only.

The NOEL for ChE is 6.0 ppm.

6. Urinalysis^

Urine was collected from fasted animals at same intervals as blood. The CHECKED (X) parameters were examined.

| X | | X | |
|---|---|---|---|
| | Appearance* | X | Glucose* |
| X | Volume* | X | Ketones* |
| X | Specific gravity* | | Bilirubin* |
| X | pH | X | Blood* |
| X | Sediment (microscopic)* | | Nitrate |
| X | Protein* | | Urobilinogen |

^Not required for subchronic studies
* Required for chronic studies

Results - The results of urinalysis were not remarkable at the various sampling intervals in treated males and females in comparison to controls.

The NOEL is 120 ppm (HDT).

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

| X | | X | | X | |
|---|---|---|---|---|---|
| Digestive system | | Cardiovasc./Hemat. | | Neurologic | |
| X | Tongue | X | Aorta* | XX | Brain*+ |
| X | Salivary glands* | XX | Heart* | X | Periph. nerve*# |
| X | Esophagus* | X | Bone marrow* | X | Spinal cord (3 levels)*# |
| X | Stomach* | X | Lymph nodes* | X | Pituitary* |
| X | Duodenum* | XX | Spleen | X | Eyes (optic n.)*# |
| X | Jejunum* | X | Thymus* | Glandular | |
| X | Ileum* | Urogenital | | X | Adrenal gland* |
| X | Cecum* | XX | Kidneys*+ | | Lacrimal gland# |
| X | Colon* | X | Urinary bladder* | X | Mammary gland*# |
| | Rectum* | XX | Testes*+ | X | Parathyroids*++ |
| XX | Liver *+ | X | Epididymides | X | Thyroids*++ |
| | Gall bladder* | X | Prostate | Other | |
| X | Pancreas* | X | Seminal vesicle | X | Bone*# |
| Respiratory | | X | Ovaries*+ | X | Skeletal muscle*# |
| X | Trachea* | X | Uterus* | X | Skin*# |
| X | Lung* | | | X | All gross lesions and masses* |

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
\# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. Organ weight - There were no compound-related effects in absolute or relative organ weights of spleen, liver, kidneys, heart, testes/ovaries, and brain of treated male and female rats in comparison to controls. The NOEL is 120 ppm (HDT).

b. Gross pathology - There were no compound-related effects in gross necropsy findings in treated male and female rats in comparison to controls. The NOEl is 120 ppm (HDT).

c. Microscopic pathology

1) Non-neoplastic -

1. Pancreas

| | Females | | | |
|---|---|---|---|---|
| Dose (ppm) | 0 | 6 | 12 | 120 |
| No. examined | 55 | 55 | 55 | 55 |
| atrophy exocrine, focal | 3 | 3 | 11 | 11 |



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Although there is an increase in this lesion at 12 and 120 ppm, the incidences at 0 and 6 ppm are unusually low. In comparison, males had 12, 14, 14, 9 in the control, low, mid and high-dose groups. Additionally, there was no increase in the severity of the grade of the lesion with dose.

Age-adjusted incidences of this lesion in the pancreas are shown below:

Pancreas

Females: Atrophy, exocrine focal

| Dose (ppm) | A. N. | Week on Study | Grade |
|---|---|---|---|
| 0 | 63 | 95 | 1 |
| 0 | 99 | 75 | 1 |
| 0 | 94 | TK | 1 |
| 6 | 174 | 92 | 1 |
| 6 | 178 | 74 | 1 |
| 6 | 216 | 107 | 1 |
| 12 | 278 | 98 | 1 |
| 12 | 280 | 97 | 1 |
| 12 | 285 | 94 | 1 |
| 12 | 312 | 85 | 1 |
| 12 | 330 | 97 | 1 |
| 12 | 290 | TK | 1 |
| 12 | 297 | TK | 2 |
| 12 | 299 | TK | 1 |
| 12 | 307 | TK | 1 |
| 12 | 310 | TK | 1 |
| 12 | 311 | TK | 1 |
| 120 | 397 | 91 | 1 |
| 120 | 387 | TK | 1 |
| 120 | 395 | TK | 1 |
| 120 | 398 | TK | 1 |
| 120 | 401 | TK | 1 |

| | | | |
|---|---|---|---|
| 120 | 406 | TK | 1 |
| 120 | 407 | TK | 1 |
| 120 | 412 | TK | 1 |
| 120 | 413 | TK | 1 |
| 120 | 422 | TK | 1 |
| 120 | 425 | TK | 1 |

Earliest week of lesion is week 74 in low-dose group (6.0 ppm).

No. Female Rats Dying Before Week 74

| Dose (ppm) | No. Rats | At Risk No. Examined |
|---|---|---|
| 0 | 15 | 40 |
| 6 | 16 | 39 |
| 12 | 10 | 45 |
| 120 | 4 | 51 |

Effective Proportions

| Dose (ppm) | 0 | 6 | 12 | 120 |
|---|---|---|---|---|
| No. examined | 40 | 39 | 45 | 51 |
| No affected atrophy, exocrine gland, pancreas | 3 | 3 | 11 | 11 |
| % | 7.5% | 7.7% | 24.4% | 21.5% |

Based on the results of effective proportions, the NOEL is 6.0 ppm and the LEL is 12.0 ppm.

2. Lung

| Dose (ppm) | 0 | 6 | 12 | 120 |
|---|---|---|---|---|
| No. examined | 55 | 55 | 55 | 55 |
| Sex | | | | |
| Lympho-reticular proliferation | | | | |
| Males | 0 | 3 | 1 | 9 |
| Females | 2 | 0 | 2 | 7 |

The lesion is not dose-related and there was no increase in the severity of the grade of the lesion at the high-dose. The lesion is essentially an age-related lesion and is present at increased incidences at the high-dose in both sexes due to the improved survival of both sees at the high-dose. Age-Adjusted incidences of this lesion in the lung are shown below:

Lung: lymphoreticular proliferation

| Dose (ppm) | A. N. | Week on Study | Grade |
|---|---|---|---|
| **Males** | | | |
| 6 | 141 | 77 | 1 |
| 6 | 134 | TK | 1 |
| 6 | 150 | TK | 1 |
| 12 | 264 | TK | 1 |
| 120 | 335 | TK | 1 |
| 120 | 337 | TK | 1 |
| 120 | 340 | TK | 1 |
| 120 | 341 | TK | 1 |
| 120 | 356 | TK | 1 |
| 120 | 357 | TK | 1 |
| 120 | 360 | TK | 1 |
| 120 | 368 | TK | 1 |
| 120 | 376 | TK | 1 |
| **Females** | | | |
| 0 | 70 | 44 | 1 |
| 0 | 73 | TK | 1 |
| 12 | 297 | TK | 1 |
| 12 | 319 | TK | 1 |
| 120 | 403 | 93 | 1 |

| | | | |
|---|---|---|---|
| 120 | 435 | 93 | 1 |
| 120 | 396 | TK | 1 |
| 120 | 402 | TK | 1 |
| 120 | 413 | TK | 1 |
| 120 | 414 | TK | 1 |
| 120 | 422 | TK | 1 |

Earliest death is in week 44 in control female and week 77 in 6.0 ppm male.

No. Males Dying Before Week 77

| Dose (ppm) | Number Dying | At Risk No. Examined |
|---|---|---|
| 6 | 10 | 45 |
| 12 | 21 | 34 |
| 120 | 16 | 39 |

No. Females Dying Before Week 44

| Dose (ppm) | Number Dying | At Risk No. Examined |
|---|---|---|
| 0 | 0 | 55 |
| 12 | 1 | 54 |
| 120 | 0 | 55 |

Effective Proportions

| Males | | | | |
|---|---|---|---|---|
| Dose (ppm) | 0 | 6 | 12 | 120 |
| No. affected | 0 | 3 | 1 | 9 |
| No. examined | 55 | 45 | 34 | 39 |
| % | 0 | 6.7% | 2.9% | 23.1% |
| **Females** | | | | |
| Dose (ppm) | 0 | 6 | 12 | 120 |
| No. affected | 2 | 0 | 2 | 7 |
| No. examined | 55 | 55 | 54 | 55 |
| % | 3.6% | 0 | 3.7% | 12.7% |

Based on the results of effective proportions, the NOEL is 12.0 ppm and the LEL is 120 ppm.

2) Neoplastic

1. Pancreas

| | Females | | | |
|---|---|---|---|---|
| Dose (ppm) | 0 | 6 | 12 | 120 |
| No. examined | 55 | 55 | 55 | 55 |
| islet cell hyperplasia | 0 | 1 | 1 | 2 |
| adenoma | 0 | 3 | 3 | 4* |
| % | 0 | 5.4 | 5.4 | 7.2 |

* $p > 0.05$

The occurrence of this tumor in treated female groups is not considered compound-related since it is not statistically significant. Charles River CD rats (female) have a range of 0-4% and a mean of 0.9% for islet cell adenomas.

Islet Cell
Females Pancreas

| Dose ppm | A.N. | Weeks | Tumor |
|---|---|---|---|
| 6 | 203 | 100 | adenoma |
| 6 | 177 | TK | adenoma |
| 6 | 202 | TK | adenoma |
| 12 | 297 | TK | adenoma |
| 12 | 298 | TK | adenoma |
| 12 | 307 | TK | adenoma |
| 120 | 389 | TK | adenoma |
| 120 | 407 | TK | adenoma |
| 120 | 408 | TK | adenoma |
| 120 | 440 | TK | adenoma |

As can be seen from the above table, the islet cell adenomas were all, except one, present at terminal kill in week 109.

| | Males | | | |
|---|---|---|---|---|
| Dose (ppm) | 0 | 6 | 12 | 120 |
| No. examined | 55 | 55 | 55 | 55 |
| islet cell hyperplasia | 0 | 1 | 1 | 2 |
| adenoma | 3 | 0 | 0 | 2 |
| % | 5.4 | | | 3.6 |
| islet cell carcinoma | 1 | 0 | 0 | 0 |
| % | 1.8 | | | |

The control group in males had a higher occurrence of tumors than treated groups. Charles River CD Rats (male) have a range for adenomas of 0-8% (mean 3.8%) and for carcinomas, the range is 0-9% (mean 1.6%).