6-18-80

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

MEMORANDUM

OFFICE OF TOXIC SUBSTANCES

SUBJECT: EPA Reg.#11273-EUP-19; Propetamphos; PP#0H5260; Request for temporary food additive tolerance of 0.1 ppm in or on food and experimental use permit for use in handling establishments. CASWELL#706A; Accession#242459 - 462

FROM: William Dykstra
Toxicology Branch, HED (TS-769) WHD 6/18/80

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

& Residue Chemistry Branch
(TS-769)

Recommendation:

1) The submitted toxicology studies are acceptable as core-minimum data.

2) The EUP and temporary food additive tolerance are not toxicologically supported. The maximum theoretical residue concentration of .15 mg/day from the proposed tolerance of 0.1 ppm in food exceeds the provisional maximum permissable intake of 0.03 mg/day, based on the NOEL of 2 ppm in the six-month dog study and using a 100 fold safety factor, by a factor of 5 .

3) A 10 fold safety factor for cholinergic effects is used for a 2-year dog study.

Confidential Statement of Formulation

Safrotin 4 EC Insecticide

Ingredient	Percent Weight
propetamphos, technical	55.0 A.I.
[redacted]	
	100.0

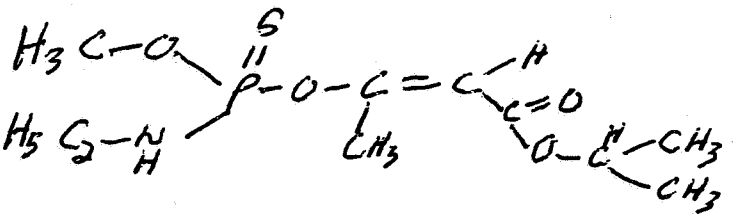
Inerts cleared under 180.1001.

6 pages

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Chemical Name: (E)-1-methylethyl-3-[[ethylamino)methoxy phosphinothioyl] oxy]-2-butenoate

Chemical Structure:



EUP Program

Dates: August, 1980 through August, 1981

Locations:

Type of Establishment	Possible Sites	Number of Tests
Food Service	Delicatessen N. New Jersey; Grocery Store, N. New Jersey	1-2
Manufacturing Plant	Bakery, N. New Jersey; Pizza Plant, N. New Jersey; Food mix plant, N. New Jersey; Ice cream plant, N. New Jersey	2
Processing Plant	Dairy, N. New Jersey Spice plant, N. New Jersey; Coffee plant, N. New Jersey.	1-2

Review:

New toxicological data submitted.

1. 6-month Feeding Study in Dogs (Sandoz, Agro Dok CBK 3825/79, Report No. TOX 21/79)

   Test Material: San 52.139 I

   32 beagle dogs, 16 of each sex, were divided into four groups. The age ranged between six and eight months. The animals were immunized against distemper, hepatitis, leptospirosis and rabies. Before starting the study, the dogs were kept for a 5-week period in order to get them accustomed to their new environment. They were caged individually and had free access to feed and water. Each dosage group

consisted of four males and four females. The compound was mixed into the powered standard dog diet by means of a Turbula mixer to provide the desired mixture. The controls received the pure diet.

The dose groups were:

	Begin of Study		After Six Weeks
	controls		controls
(Low dose)	6 ppm	(Low dose)	2 ppm
(Mid dose)	12 ppm	(Mid dose)	4 ppm
(High dose)	24 ppm	(High dose)	24 ppm

The physical examination included: weekly body weight, neurological, oral and behavioral inspection. The food consumption was recorded daily. The volumes in hematology and clinical chemistry were assessed with all animals before initiating the study (weeks-3 and -2, pre-tests) and after 1, 2, 3, and 6 months on test. The BSP liver function test was estimated before treatment began and at the end of the study. Urine was analyzed in weeks -2 (pre-test), 4, 8, 12 and 27.

Opthalmoscopic examinations of both eyes were performed shortly before the beginning of the study and after 6 months on test. The activity of blood cholinesterase (plasma and RBC) activity was determined at weeks -3 and -2 (pretest) and at weeks 4, 6, 8, 12, 20, and 26. The activity of the cholinesterase in the brain and liver and the induction of drug metabolizing enzymes was performed in the liver after the animals had been killed with Nembutal and necropsied after 28 weeks. The appearance of the organs and tissues was then noted and their weights recorded. Parametric and non-parametric statistical tests were employed to assess the significance of inter-group differences of the data.

Results:

All animals, controls as well as treated groups, were in good condition during the whole study. The coats were sleek and the mucous membranes were supplied with blood in a normal manner. The behavior was normal. The dogs were vivacious and moved normally.

Neither between the controls and treated male and female dogs were there significant differences in body weight gain. In the males, the average food intake was highest in the control group and lowest in the high-dose group. In the females, the low-dose group showed tha highest food consumption and the mid-dose group the lowest.

The average daily water consumption showed deviations which were not dose-related.

In the hematological measurements in the males, there were no significant dose-related deviations compared to the controls. The females in the high-dose group showed an increase of WBC in the pre-test period and after 4, 12, and 26 weeks. The MCHC value in the high dosage group was elevated in week 4. No other hematological alterations were observed.

The mean values and single values of glucose, BUN, creatinine, bilirubin and of cholesterol were normal in all groups and did not noticeably differ from the pre-test data. The uric acid concentrations were particulary low in all animals, so the measurement was difficult and submitted to variations.

Total protein concentrations were relatively high in males and females in week 4 and in females only in week 12 and 26, but there were no treatment-related variations. The reduced albumin concentration (vs. controls) in the females of the mid and high dose in weeks 8 and 12 are considered normal as compared to the pre-test values. This is confirmed by the results obtained after 26 weeks.

In the electrolytes of the blood plasma the values of some parameters, like chlorides or inorganic phosphorus, were subject to noticeable variations from one determination to the other and some statistically significant differences to the controls could be observed.

Thus a low control mean value was found for calcium in the females in week 8 and for chlorides in the pre-test (week -1) for both males and females. Phosphorus concentrations were particulary low in females in week 4 (controls and mid group). In the males, sodium intergroup differences showed significant deviations in the pre-test only. In week 26 one high-dose male showed abnormal Na^+ (decreased) and K^+ values (increased), but a normal chloride; a high dose female had Na^+ increased. At the last measurement, the sample from high-dose female 32 was spilled unintentionally so that the electrolytes could not be measured. All other values varied within the limits of the normal ranges and a compound-related effect was not observed.

The activity of the plasma-ChE was clearly decreased in both males and females in the high-dose (24 ppm), mid dose (12 ppm) and low dose (6 ppm), before these dosages were changed. After the dosage reduction was carried out to 2 ppm (low) and 4 ppm (mid), the plasma-ChE recovered the activity returned to within normal limits. The RBC-ChE was clearly inhibited in the high-dose group (24 ppm) and mid-dose group (12 ppm) at week 4 and 6. When the mid-dose group was changed to 4 ppm at week 6, the RBC-ChE was significantly inhibited at weeks 8 and 12 but not weeks 20 and 26. No significant inhibition of RBC-ChE was noted at the low-dose of 6 ppm (six weeks) or 2 ppm (remainder of study).

SGPT and SGOT as well as LDH showed normal activities all along the study, with the exception of the male control for SGPT which was slightly increased at the end of the study. For SAP, the activity of the low-dosed males increased more than in the other treated groups; in the females the SAP activities were similar in all control and treated groups.

The BSP liver function test showed normal retention rates which, after 26 weeks on test, did not significantly differ from the pre-test figures.

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The ChE activity in the homogenates of cerebellum samples was not significantly different from controls, and no dose-related trend was evident. In the cortical region of the brain, the ChE of the homogenates was seen to be dose-dependently decreased in males in the mid- and high-dosed groups, and in high-dosed females.

In liver homogenates, the mid- and in high-dosed groups showed the activity of the acetyl-ChE was slightly less decreased than the butyryl-ChE and in males less than females. In these groups the ChE activity was dose-dependently lowered.

In the urinanalysis, only the pH-value and specific-gravity was lowered in the middle dosage of the males in the pre-test period. All other values were within a normal range. No special findings in correlation with the dosage or duration of the study were observed in the ophthalmoscopic evaluations. At necropsy, there were no macroscopic changes or lesions and organ weights were unaffected by treatment.

Histopathological investigations demonstrated no treatment-related microscopic changes.

Conclusion: The NOEL is 2 ppm for the 6-month dog study. The LEL is 4.0 ppm in the diet for ChE inhibition.

Classification: Core-Minimum Data

2) 13-Week Feeding Study in Rats (Sandoz LTD, AGRO DOK CBR 2554/77, Report No. 24/77)

Test Material: Propetamphos, San 52.139I

120 SPF Sprague-Dawley rats (OFA-strain), 4-5 weeks old at the beginning of the study were divided into 4 groups of 15 males and 15 females each.

The dietary levels were:

control	0 ppm
low-dose	2 ppm
mid-dose	4 ppm
high-dose	8 ppm

One male in the high-dose died in week 4, the cause of death is unknown. All other animals survived after 13 weeks without any symptoms. The animals were observed daily for symptoms and behavior. Body weight and food consumption of the animals were recorded weekly.

The following investigations were carried out on 10 rats per dose group (5M + 5F) after 4, 8 and 13 weeks on test hematology, blood chemistry (RBC ChE was also measured in the erythrocytes and after 1 and 2 weeks on test), urinalysis except in week 8. At the end of the test, 10 animals per sex and dose were killed with Nembutal (1 ml/kg, i.p.) and

necropsied. The organs were inspected, weighed adn prepared for histopathological examination.

ChE activity was investigated in brain and liver homogenates of 5 animals per sex and dosage.

After necropsy, all remaining rats received a non-treated died for a recovery period of 4 weeks. Then plasma and RBC ChE were again estimated.

Parametric and nonparameteric tests were used to assess the significance of intergroup differences.

Results:

No overt signs of cholinergic poisoning were observed. All animals showed normal behavior. One male in the high dose died on week 4, the cause of death is unknown. Body weight gain and food consumption were unaffected by treatment. The hematological and urinary investigations showed normal values in all groups. Slightly lower activity in the plasma ChE was observed in female rats only during the first two weeks of study. In the males, there were no significant difference between control and treated animals. The enzymatic activity of the RBC ChE were slightly lower on rats receiving the 8 ppm diet. The ChE of the brain and liver were not significantly influenced by the administered diet. Other clinical chemistry parameters were unremarkable.

At necropsy, no pathological observations were noted and organ weights were noted and organ weights were normal. The microscopic histopathological examinations revealed no treatment related lesion in any organ or tissue.

Conclusion: The NOEL is 4 ppm based on RBC ChE inhibition. The LEL is 8 ppm based on RBC-ChE inhibition.

Classification: Core-Minimum Data

3) Conclusions and Recommendations:

The Theoretical Maximum Residue Contribution (TMRC) from a proposed temporary tolerance of 0.1 ppm in 1.5 kg of food is 0.15 mg/day. The provisional maximum permissable intake is based on the NOEL of 2 ppm in the 6-month dog study, using a 100* fold safety factor.

$$ADI = 2 \text{ ppm} \times .025 \text{ mg/kg/day} = .05 \div 100 = .00050 \text{ mg/kg/day}$$

$$PMPI = .00050 \text{ mg/kg/day} \times 60 = .030 \text{ mg/day}/1.5 \text{ kg}$$

Therefore the TMRC exceeds the PMPI by a factor of 5.0.

*New Concepts in Safety Evaluation, Chapter 4, Halsted Press Book, 1976.

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