UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CASWELL#706A

DATE: July 2, 1979

SUBJECT: Propetamphos EPA Registration#11273-ER (Propetamphos for manufacturing use only; 11273-EE (Safrotin™ 4 Emulsifiable Concentrate Insecticide).

FROM: William Dykstra, Ph.D
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TO: Ms. M. Mautz
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Registrant: Sandoz, Inc.
Crop Protection
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Recommendations:

1. The neurotoxicity study with technical propetamphos (IBT No. 651-06763) is required to be validated by EPA procedures or repeated according to presently proposed EPA guidelines.

2. The label for Safrotin 4 EC contains the human hazard signal words WARNING and DANGER. The correct label signal word is Warning.

3. The proposed Sandoz Technical bulletin needs to be changed on the basis of referenced and submitted toxicity data. The Toxicology section of the bulletin should indicate that 4 EC is a eye irritant (TOX II: WARNING) and not "not an irritant".

   The neurotoxicity reference cannot be used at this time. The referenced or submitted Toxicology studies did not contain a 28 day rat oral study with a NEL of 10 ppm. The registrant must reference or submit this study for evaluation.

4. The referenced and submitted toxicology studies are acceptable as core minimum data and support the registration of 11273-ER and 11273-EE.

Review:

A. Toxicity Data previously submitted and accepted in Accession#228723 are summarized below:

   1. Reference 1. Acute toxicity studies in rats and rabbits)IRDC, 163-254, April 30, 1974)

      Test Material: VEL-4283, Technical Batch A 3896; yellow brown liquid.

   a. Acute oral toxicity (LD50) in male and female albino rats.

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male albino rats: 75.4 (60.2 - 94.4) mg/kg
female albino rats: 82.8 (66.1 - 103.7) mg/kg

Combined male and female rats: 79.1 (67.9 - 92.2) mg/kg

Classification: Core-Minimum Data; TOX II: WARNING

b. Acute inhalation Toxicity (LC50) in albino rats.

male albino rats: 19.3 (15.5 - 23.9) mg/L
female albino rats: 15.4 (11.7 - 20.3) mg/L

Combined male and female rats: 17.0 (14.9 - 20.1) mg/L

Classification: Core-Minimum Data; TOX III: CAUTION

c. Acute dermal (LD50) in albino rabbits.

male albino rabbits: 474 (356 - 633) mg/kg
female albino rabbits: 474 (356 - 633) mg/kg

Combined male and female albino rabbits: 474 (323 - 696) mg/kg

Classification: Core-Minimum Data; TOX II: WARNING

d. Primary skin irritation.

P.I. = 0.3

Classification: Core-Minimum Data; TOX IV: CAUTION

e. Primary eye irritation

No corneal opacity; conjunctivitis

Classification: Core-Minimum Data; TOX III: CAUTION

2. Reference 2. Acute toxicity studies in rats and rabbits (IRDC, 163-255, May 8, 1974)

Test Material: VEL-4283, 4EC; yellow brown liquid.

a. eye irritation test in albino rabbits Group 1 - 5 minutes wash (5 rabbits)
corneal opacity in 3/5 rabbits at 72 hours and 1/5 rabbits at 7 days.

Group 2 - 24 hour wash (3 rabbits)
corneal opacity in 1/3 which persisted for 7 days.

Classification: Core-Minimum Data; TOX I: DANGER

b. primary skin irritation in rabbits
P.I. = 1.7

Classification: Core-Minimum Data; TOX IV: CAUTION

c. Acute dermal toxicity in albino rabbits
LD50 between 200 - 2000 mg/kg

Classification: Core-Minimum Data; TOX II: WARNING

d. Acute inhalation LC50 in albino rats
LC50 between 2.0 - 200 mg/L for 4 hour

Classification: Core-Minimum Data; TOX III: CAUTION

f. Acute oral toxicity (LD50) in male and female albino rats

male albino rats: 149.3 (116.8 - 190.8) mg/kg
female albino rats: 90.8 (75.6 - 109.1) mg/kg

Combined male and female rats: 114.2 (95.8 - 136.1) mg/kg

rence 3. Acute toxicity studies in rats and rabbits (IRDC, 163-378, 4, 1975)

Material: VEL-4283 4EC Diluted for use (1.25 oz/gal)

a. eye irritation test in albino rabbits
Group 1 - 5 minute wash (5 rabbits)
no corneal opacity; irritation reversible by 72 hours;
Core-Minimum Data; TOX III: CAUTION

Group 2 - 24 hour wash (3 rabbits)
no corneal opacity; irritation reversible in 48 hours;
Core-Minimum Data; TOX III: CAUTION

b. primary skin irritation in rabbits
P.I. = 0.1; Core-Minimum Data; TOX IV: CAUTION

c. Acute dermal toxicity in albino rabbits
LD50 > 2000 mg/kg
Core-Minimum Data; TOX Category III: CAUTION

d. Acute inhalation toxicity in albino rats
LC50 > 200 mg/kg
Core-Minimum Data; TOX IV: CAUTION

e. Estimated Acute Oral Toxicity (LD50) in male and female rats.

male albino rats: 13,528 (10,787 - 16,966) mg/kg
female albino rats: 10,253 (8874 - 11,846) mg/kg

Combined male and female rats: 11,778 (10,227 - 13,564) mg/kg

Classification: Core-Minimum Data; TOX IV: CAUTION

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5. Reference 5. Acute oral toxicity study in ALbino Rats (IRDC, July 2, 1975)

Test Material: VEL-4283 Emulsifiable Concentrate Insecticide, 4 lbs A.I. per gallon

The compound was administered to Four groups of 20 rats (10 M & 10 F) of Charles River Strain at dosage levels of 25, 50, 75 and 100 mg/kg.

Pharmacodynamic signs were obtained following dosing.

Cholinesterase values (plasma and RBC) were determined on 5 male and 5 female rats from each group during the control period and at 24 and 48 hours and 7 days. Cholinesterase values were determined on the remaining 5 male and 5 female rats at 24 hours and 7 days following compound administeration.

Results: All surviving rats in the 25, 50 and 75 mg/kg dosage level groups exhibited normal body weight gains during the study period. Male rats which received the 100 mg/kg dosage level of the test compound exhibited a less than normal body weight gain. Female rats at this dosage level exhibited a group average loss in body weight gain during the study period. Examination of the cholinesterase levels (plasma and RBC) in those rats examined at 24 and 48 hours and at 7 days, revealed a decrease in the values obtained for plasma in those groups which received 50, 75 and 100 mg/kg at 24 and 48 hours. At 7 days these values had returned to control value level. In those rats for which choinesterase values were determined at 24 hours and 7 days, a similar decrease was observed in plasma values from all treated groups at 24 hours. At 7 days, these animals also showed control plasma cholinesterase values. The decrease in plasma cholinesterase values observed was dose-related at those intervals. No significant effect was observed on RBC cholinesterase values during the study period.

Conclusion: The NOEL for plasma cholinesterase inhibition for acute dosage is 25 mg/kg. At 50, 75 and 100 mg/kg, plasma cholinesterase was inhibited in a dose-dependent manner but returned to normal by day 7. No effect was observed on RBC cholinesterase values during the study period.

Classification: Core-Minimum Data

6. Reference 6. Three-Week Dermal Study in Rabbits (IRDC, 163-373, Jan. 12, 1976)

Test Material: Tech Vel-4828, 20 grams

In a dermal study using NZW rabbits, tech Vel-4828 was applied 6 hours per day at dosage levels of 0.5, 2.5 and 5.0 mg/kg/day, 5 days a week for 3 weeks. Four male and Four female rabbits were used at each dosage level and also in a control group. The rabbits were observed daily and individual body weights were recorded weekly. Hematological, biochemical and urinanalysis studies were recorded once in the control period and at 21 days of study. Plasma and RBC cholinesterase activity was determined for all rabbits once in the control period and on days 4, 7, 11, 18 and 21 of study. Gross pathological examination, organ

weights and histolopathology of tissues was performed on all rabbits. All statistical analyses compared the treatment groups with the control groups. The body weights, hematological and biochemical parameters and cholinesterase activity were compared by analysis of variance (one-way classification) as described by Steel and Torrie. Then Bartlett's test for homogeneity of variance as described by Steel and Torrie was applied to the respective parameters. The appropriate t-test (for equal or unequal variances) as described by Steel and Torrie was used to judge the significance of difference between the means based upon Dunnett's multiple comparison tables.

Results: Dermal Irritation considered to be related to the compound included atonia for rabbits at 0.5 mg/kg/day dosage level, edema, atonia, coriaceousness, desquamation and occasional fissuring for rabbits at the 2.5 mg/kg/day dosage level and atonia, coriaceousness, and ocassionally blanching or slight bleeding for rabbits at the 5.0 mg/kg/day dosage level. One rabbit at the 0.5 mg/kg/day dosage level, one rabbit at the 2.5 mg/kg/day, and 3 rabbits at the 5.0 mg/kg/day showed slight to moderate losses of body weight during the study. The controls and other treated rabbits generally maintained body weight during the study. One rabbit at the 2.5 mg/kg/day dosage level died following collection of blood on the 21st day of study. One rabbit at 0.5 mg/kg/day dosage level and 2 rabbits at the 5.0 mg/kg/day dosage level showed moderate to marked decrease in the number of erythrocytes, hemoglobin concentration and hematocrit. No changes or unusual values were seen in biochemical studies or urinanalysis. At the 0.5 mg/kg/day dosage level, RBC cholinesterase activity was decreased for most of the rabbits at day 4 and for a few of the rabbits at day 7. At the 2.5 mg/kg/day dosage level, RBC cholinesterase was decreased for most of the rabbits on day 4, 7, 11 and for a few rabbits on day 18. At the 5.0 mg/kg/day dosage level, decreased RBC cholinesterase activity was noted for most of the rabbits on days 4, 7, 11 and 14 and for a few of the rabbits on days 18 and 21. Decreases in plasma cholinesterase activity were seen sporadically for some of the treated rabbits, however, decreased plasma cholinesterase activity was noted for most of the rabbits at the 2.5 and 5.0 mg/kg/day levels on days 11 and 18 of the study.

No compound related gross pathologic lesions or variations in organ weights were observed in any rabbits from the experimental group. Evidence of skin irritation, characterized by acanthosis, hyperKeratosis and dermal inflammatory infiltrate with occassional epidermal necrosis and abscessation of hair fullicles occurred in all rabbits from the treated groups and the control groups which received corn oil. Hence, the skin lesions in treated rabbits were attributed to the corn oil used as a vehicle for Tech VEL-4283. An acute inflammatory infiltrate was present in the lymph nodes draining the application site of most rabbits from the corn oil control and the treated groups, and was considered treatment-related.

Intratubular giant cells occurred in the testes of 2 male rabbits in the 0.5 mg/kg/day group and 1 rabbit in the 2.5 mg/kg/day group. In the absence of this lesion at 5.0 mg/kg/day level, its significance is questionable.

Occurrence of degenerated seminiferous tubules in the testes of 3 rabbits from 0.5 mg/kg/day group was not considered significant in as much as a similar lesion occurred in a control rabbit.

Conclusion: Tech VEL-4283 produces transient RBC cholinesterase depression in a dose-dependent.

Classification: Core-Minimum Data

7. Reference 7. Twenty-one day Dermal study in Albino Rabbits (IRDC, 163-335, Aug. 25, 1975)

Test Material: VEL-4283 Emulsifiable Concentrate Insecticide, 4 lbs A.I./gallon

In a 21-day dermal study in albino rabbits, the test animals (4 M & 4 F) received VEL-4283 at dosage levels of 20, 60 or 80 mg/kg/day. The test compound was applied for 6 hours each day, 5 days a week. A control group of rabbits received saline without the test compound in a manner identical to that employed for the test group.

Each rabbit was observed daily for changes in behavior and appearance and for signs of systemic toxicity and mortality. Individual body weights were obtained weekly. Signs of dermal irritation were recorded daily prior to and following each 6 hour application period.

Hematological, biochemical and urinanalyses were conducted once in the control period and at 21 days of study. Cholinesterase levels in plasma and RBC were determined on all rabbits once in the control period and on days 4, 7, 11, 14, 18 and 21 of the study period. Gross pathology and histopathology were performed on all rabbits.

Results: Clinical signs observed during the study period which were considered compound related included ataxia, fasiculations, dyspnea, respiratory congestion, prostration, cyanosis, convulsions, cachexia, flaccidity and vocalization. Seven of 8 rabbits at 60 mg/kg/day dosage level died during the study. All of the animals at the high dosage level, 180 mg/kg/day, died or were sacrificed in extremis by the 8th day.

Dermal irritation noted included erythema, edema, atonia, desquamation, lethery texture and fissuring, all of which were observed in tabbits in each of the three treated groups. No significant difference was noted in the findings obtained prior to and following the 6 hour daily application period or between intact and abraded animals.

No changes in body weights occurred which were considered compound related. Hematological, biochemical and urinanalysis studies at 21 days of the study period did not reveal compound related changes.

A decrease in plasma and RBC cholinesterase values was obtained from rabbits in each of the treated groups. The decrease in cholinesterase value noted was attributable to compound application.

Except for skin changes noted above, no compound related gross or pathologic lesions or organ weights were observed at necropsy in the 8 rabbits from the 20 mg/kg/day group and the 1 rabbit from the 60 mg/kg/day group which survived to the terminal sacrifice.

Rabbits dying or sacrificed in extremis at 60 and 180 mg/kg/day had evidence of gastrointestinal irritation and pneumonia; both of these conditions were considered directly or indirectly compound related.

Compound related microscopic lesions observed included acanthosis, hyperKeratosis, and dermal inflammation in the skin of most rabbits at all 3 dosage levels, fiber degeneration in skeletal muscles in several rabbits at all 3 levels and pneumonia in several rabbits from the 60 and 180 mg/kg/day levels.

Conclusion: Vel-4283 produces cholinergic effects at 20, 60 and 180 mg/kg/day.

Classification: Core-Minimum Data

8. Reference 8. Three-Week Dermal Study in Rabbits (IRDC, 163-372, Jan. 22, 1976)

   Test Material: The compound was a yellow brown liquid; VEL-4283 4 E.C., 100 grams

   In a dermal study using NZW rabbits, VEL-4283-4EC was applied at dosage levels of 1, 5 and 10 mg/kg/day, 6 hours a day, 5 days a week, for 3 weeks. Four male and Four female rabbits were used at each dosage level and also in a control group. The rabbits were observed daily and individual body weights were recorded weekly. Hematological, biochemical and urinanalysis were conducted once in the control period and at 21 days of study. Plasma and RBC cholinesterase activity was determined for all rabbits once in the control period and on days 4, 7, 11, 14, 18 and 21 of study. Gross pathology, organ weights and histopathology were performed on all rabbits.

Results: No dermal irritation or changes in general behavior and appearance comsidered to be related to compound were seen. No changes considered related to compound were seen in body weights, hematological and biochemical studies or urinanalyses. Decreased RBC cholinesterase activity was noted only sporadically (1 or 2 rabbits on 1 or 2 days) for rabbits at the 1 mg/kg/day dosage level. At the 5 mg/kg/day dosage level, decreased RBC cholinesterase was noted for a few rabbits on days 7 and 18 and for most of the rabbits on days 11 and 14.

Results: Rats exposed at the 3 and 5 mg/L concentrations exhibited body weight losses which were considered related to compound administration. Rats at the 1 mg/L exposure level showed body weight gains which were equivalent to those experienced in the control group.

Food consumption values were similar for the control and treated rats at all 3 exposure levels. Four rats at the 3 mg/L exposure level and 6 rats at the 6 mg/L exposure level died or were sacrificed in extremis.

Hematological and urinanalyses studies did not reveal compound related changes. One rat at the 3 mg/L exposure level and 1 rat at the 6 mg/L exposure level exhibited elevated glucose, urea nitrogen, SGOT and SGPT values. In addition, several rats at each of the 3 exposure levels exhibited elevated SGOT values plasma.

Cholinesterase values were decreased during the study period at all exposure levels in both male and female rats. The effect obtained was dose-related. Decreased cell (RBC) cholinesterase values also were obtained during the study period at each of the 3 exposure levels used. This effect was evident in both male and female animals and was dose-relared at 14 days.

No compound related gross or microscopic pathologic lesions or organ weight variations were observed in any rats from 1 mg/L exposure level. At the 3 and 6 mg/L levels, stomach hemorrhage and stomach mucosal thickening were observed in several rats and were considered compound related stomach mucosal necrosis and/or ulcertain and bone marrow hyperplasia occurred in a small muber of rats at the 3 and 6 mg/L levels. All deaths during the study were attributed to compound effect.

Conclusions: Dose-related cholinesterase inhibition (plasma & RBC) occurred at 1, 3 and 6 mg/L.

Classification: Core-Minimum Data

10. Reference 10. Pilot Rabbit Teratology Study (IRDC, 163-344, Sept, 3, 1975)

Test Material: VEL-4283, 94% Technical

In a pilot study in Dutch Belted rabbits , Vel-4283 was administered by oral intubation at dosage levels of 5, 10, 20, 40, 80 and 160 mg/kg/day on days 6 through 18 of gestation. A minimum of four rabbits were used at each dosage level and also as a control group. Cesarean sections were performed on the 28 day of gestation.

Results: VEL-4283 was maternally toxic when administered at 20, 40, 80 and 160 mg/kg/day. All the dams died in these four groups. Before death these rabbits exhibited signs of ataxia, tremors, hypoactivity, dyspnea, cachexia marked salivation and constricted pupils.

Similar signs were seen in the 5 and 10 mg/kg/day groups, but were very infrequent and seen in very few rabbits in these two groups. A slight decrease in body weight gain during gestation was seen when comparing the rabbits at 5 and 10 dosage levels to the control rabbits.

At the 10 mg/kg/day dosage level, decreased RBC cholinesterase activity was noted for most of the rabbits on days 7, 11, 14, 18 and 21 of study.

Plasma cholinesterase activity generally was decreased for most of the rabbits at the 5 mg/kg/day dosage level particularly on days 7, 11 and 18.

Plasma cholinesterase activity was decreased for most of the rabbits at the 10 mg/kg/day dosage level particularly on days 4, 11 and 18 of study.

No compound related gross pathologic lesions or variations in organ weight were observed at necropsy in any rabbits from the experimental groups. Microscopically, occurrence of intratubular giant cells of four male rabbits from the 10 and 5 mg/kg/day (3 from 10 mg/kg/day & 1 from 5 mg/kg/day) was noted. In a comparison study (163 - 373) giant cells occurred at the lower and mid-dose but not at the high dose. With the occurrence of this lesion with a non-dose related incidence in another study, this apparent dose relationship and compound relationship which occurred in this study is of questionable significance. Occurrence of groups of degenerated seminiferous tubules in the testes of several rabbits from VEL-4283 E.C. treated groups was not considered significant in as much as a similar lesion occurred in a control group.

Conclusion: The dosage level of 1 mg/kg/day produced transitory RBC cholinesterase inhibition.

Classification: Core-Minimum Data

9. Reference 9. Fourteen-Day Inhalation Toxicity Study in Rats (IRDC, 163-334, Sept. 29, 1975)

Test Material: Vel-4283 Emulsifiable Concentrate, 4 lb A.I. per gallon; yellow-brown liquid

In a 14 day inhalation study in rats, (5 M & 5 F), the test animals were exposed to VEL-4283 at concentrations of 1, 3 and 6 mg/L. The rats were exposed for 4 hours daily, 5 days weekly for 2 weeks. A control group of rats also was employed. The control received only the air flow, without the introduction of the test compound, in a manner identical to that employed for the test groups. Each rat was observed daily for changes in behavior and appearance.

Individual body weights and food consumption values were recorded weekly. Hematological, biochemical and urinanalysis studies were conducted at 14 days of study (termination) cholinesterase levels (plasm and RBC) were determined for all rats once in the control period and at 3, 7, 10, and 14 days of study. At the completion of the exposure period, all rats were sacrificed by decapitation and necropsies. Organ weights and histopathological examination were performed on the tissues.

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Conclusion: The results indicate that Vel-4283 when administered in doses of 5 and 10 mg/kg/day on days 6 through 18 of gestation had no teratogenic effect.

Classification: Supplementary DATA - pilot study

11. Reference 11. Teratology Study in Rabbits (IRDC, 163-345, Feb. 27, 1976)

Test Material: VEL-4283, 94%; batch 3896

In a teratology study in Dutch Belted rabbits VEL-4283 was administered by oral intubation at dosage levels of 1, 5 and 10 mg/kg/day on days 6 through 18 of gestation.

A negative control group received the vehicle onlt and a positive control group received thalidomide at a concentration of 150 mg/kg/day on the same regimen as treated rabbits. Twenty pregnant rabbits were used in each group except at 5 and 10 mg/kg/day where maternal deaths precluded acheiving the goal of 20 pregnant at cesarean section. All statistical analyses compared the treatment groups with the cont l groups. The number of dead or resorbed fetuses, number of fetuses with soft-tissue anomalies, number with skeletal anomalies, number with accessory ribs only, number of females exhibited dead or resorbed fetuses, number dying and pregnant, number aborting and number of litters with one or more soft-tissue or skeletal anomalies were compared using Chi-square test criterion with Yates' correction on a 2 X 2 contingency tables and/or Fischers exact probability test as described by Siegel (1956) to judge significance of difference.

In addition, in each litter the number of dead or resorbed fetuses, number of fetuses with soft-tissue or skeletal anomalies and the number of fetuses with accessory ribs only were compared by the rank sum test described by Snedecor and Cochran (1967) and Weil (1970) to judge the significance of differences. This second statistical evaluation of these data was conducted to determine if there was any litter effect as opposed to an individual fetus effect (Haseman, 1975).

The mean number of corpora lutea, implantation sites and live fetuses were compared by analysis of variance (one-way classification), Bartlett's Steel and Torrie (1960) using Dunnett's (1964) multiple comparison tables to judge the significance of differences.

The live fetal weights were compared by analysis of variance (hierarchal classification) and t-test as described by Steel and Torrie (1960) using Dunnett's (1964) multiple comparison tables to judge significance of differences.

Results: No changes in general behavior or appearance considered to be related to the compound were seen at the 1 mg/kg/day dosage level group. Respiratory congestion, and various degrees of ataxia and salivation were the most frequent, physical and behavioral changes seen in the 5 and 10 mg/kg/day dosage level groups.

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Four, 4, 8, 13 and 23 dams died during the study, respectively, in the control, thalidomide, 1, 5 and 10 mg/kg/day dosage level groups of Vel-4283.

Body weight changes for the controls and other treated groups through gestation were considered normal. Due to the number of deaths in the 5 and 10 mg/kg/day groups, body weight changes throughout gestation were not very meaningful.

There were no signs of toxicity in this investigation regarding the number of corpora lutea, implantation sites, females exhibiting resorption sites, abortions, live and dead fetuses, live fetal weight, sex ratio and fetal development.

Conclusion: VEL-4283 administered on days 6 through 18 of gestation was not teratogenic or embrolethal at the dosage levels studies, but a dose-related increase in maternal toxicity was seen with a statistically significant increase present at 10 mg/kg/day. The thalidomide positive control group produced pups with skeletal and other aberations typical of the "thalidomide effect", thus demonstrating the sensitivity of the rabbits to a teratogen.

Classification: Core-Minimum Data

12. Reference 12. Neurotoxicity Study with VEL-4283 in Chickens (IBT No. 651-06763, July 24, 1975)

    Test Material: VEL-4283, 94% A.I. Tech Batch 3896

    Acute oral toxicity - LD50 phase

    Following a 16-hour fast, each of 5 groups of hens (4 hens per group) received in corn oil 31.6, 46.4, 68.1, 100.0 and 147.0 mg/kg of test material. The results of the study showed the acute median lethal dose (LD50) to be 94.4 ± 9.6 mg/kg BW of test material.

Neurotoxicity Phase

The neurotoxicological phase employed a control and 3 test groups (T-1, T-II, T-III) of 10 birds per group.

Following a 16 hour fast, a single dose of test material was administered in corn oil at a rate of 47.2, 94.4 and 188.7 mg/kg BW to birds in groups T-1, T-II and T-III, respectively. Previously calculated doses of test material were volumetrically measured and administered via gavage to each individual animal. The procedures was repeated, following a 21-day observation period, for all birds which did not possess signs of gross neurotoxicity.

The birds were observed for mortality and possible neurotoxic reactions for 21-day periods after each dose. Body weights were recorded at 0, 21 and 42 days. Following the 2 observation periods (42 days), all surviving birds were sacrificed and subjected to gross pathological examination. Any test animals exhibiting gross signs of neurotoxicity were sacrificed in extremis in order to preserve adequate tissue samples.

Animals which died during the investigation or which were sacrificed in extremis were subjected to gross pathological examinations.

The brain, sciatic nerve and spinal cord were removed at the time of gross examination and fixed in 10% buffered formalin.

Results: A slight overall body weight depression was noted on test day 21 in Group T-II when compared to the control. Animals in test Group T-I, T-II, and T-III exhibited lethargy and ataxia within 2 to 10 hours after their respective doses of test material on day 0. The symptoms of toxicity appeared to be dose-correlated. The majority of surviving animals in Group T-II appeared normal 4 days after the first dose (on day 0). There were no neurotoxic reactions noted for any animals in test Groups T-I, T-II or T-III during the first 21 days of observation.

Animals in test Groups T-I and T-II exhibited lethargy and ataxia within 2 to 4 hours after their respective doses of test material on day 21. The symptoms of toxicity appeared to be dose-correlated.

The remaining 2 animals in Group T-II appeared normal 3 days after the second dose (on day 21). There were no neurotoxic reactions noted for any animals in test Groups T-I or T-II during the second 21-day observation period.

The control birds appeared normal throughout the entire investigation. All T-II group birds died within 30 hours after receiving their respective doses on day 0. Five T-II group test animals died during the first 21-day observation period and 3 during the second 21-day observation period.

One T-I group test animal died during the second 21-day observation period.

Group pathological examination of animals which died on test revealed no abnormal tissue alterations attributed to the ingestion of the test material.

Gross pathological examination of T-I and T-II group survivors revealed ischemia of the breast and leg muscles.

Conclusion: VEL-4283 is not a delated neurotoxic agent in this study.

Classification: Core-Minimum Data

NOTE: This is an I.B.T. study and needs to be validated for registration.

13. Reference 13. Acute oral toxicity study with VEL-4283 in female Albino Rats (I.B.T. No. 601-06764, July 11, 1975)

Test Material: VEL-4283, 94%, Batch 3896

LD50 = 56.5 mg/kg (51.13 - 62.43)

Classification: Core-Minimum Data; TOX II: WARNING

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14. Reference 14. Study of the efficacy of atropine sulfate and 2-PAM Chloride as antidotes for VEL-4283 intoxication in female albino rats (I.B.T. No. 601-06764, July 11, 1975)

Test Material: VEL-4283

Summary: The data indicate than an injection intramuscularly of atropine sulfate, 2-PAM Chloride and a combination of atropine sulfate and 2-PAM Chloride are each therapeutically effective as antidotes for acute oral intoxication with VEL-4283.

Results:

Test Material	Dose (mg/kg)	Antidote (mg/kg)	Number dead / Number tested
VEL-4283	100	none	4/4
	100	Atropine sulfate (mg/kg)	0/4
	100	2-PAM Chloride (100 mg)	1/4
	100	Atropine sulfate (100 mg) and 2-PAM Chloride	1/4

Classification: Core-Minimum DATA

B. New Toxicology Data: EPA Accession No. 235623

15. Safrotin 50 EC; Acute dermal LD50 in Rabbits (Sandoz Ltd, Agrochem. Research, AGRO DOK CBK 3156/78; 64/78, September 29, 1978)

Test Material: Safrotin 50 EC; Batch No. 4495

8 groups of Two males & Two females NZW rabbits received dosages of 250, 320, 400, 500, 640, 800, 1000 and 1250 mg/kg BW of the fur clipped trunk under an impervious cuff for 24 hours. Observation for 14 days.

Results: LD50 (both sexes) = 500 mg/kg ± 31.6 mg

Toxic Signs: not reported

Body Weight: not reported

Necropsy: not reported

Classification: Core-Minimum DATA; TOX Category II: WARNING

16. Safrotin 50 EC Diluted for use: Acute Dermal Toxicity in Rabbits (Sandoz Ltd, Agrochem. Research, AGRO DOK CBK 3157/7E; 65/7E, Sept. 29, 1978

Test Material: Safrotin 50 EC diluted with water to 2%

6 rabbits (3 M & 3 F) received 6 ml/kg BW of test material on the fur clipped backs under an impervious cuff for 24 hours. Observation for 21 days.

Results: No deaths LD50 > 6 ml/kg

Toxic Signs: slight redness on skin

Body Weight: normal weight gain

Necropsy: not reported

Classification: Core-Minimum DATA; TOX Category III: CAUTION

17. Propetamphos. Primary Skin Irritation in Rabbits (Sandoz Ltd, AGRO DOK CBK 3151/78; 59/78, Sept. 29, 1978)

Test Material: technical propetamphos purity 91.8%; Batch No. P16/17

0.5 ml of undiluted test material was applied to intact and abraded skin sites on the fur clipped trunk of 6 NZW rabbits under an impervious cuff for 24 hours. Observation and scoring at 24 and 72 hours after exposure.

Results: P.I. = 0.3; slight erythema in 2/6 intact & 1/6 abraded at 24 hours. No edema. No irritation at 72 hours.

Classification: Core-Minimum Data; TOX IV: CAUTION

18. Safrotin 50 EC. Primary Skin Irritation in Rabbits (Sandoz Ltd, AGRO DOK CBK 3155/78; 63/78, Sept. 29, 1978)

Test Material: Safrotin 50 EC; Batch No. 4495

0.5 ml of test material was applied to intact and abraded skin sites on the fur clipped trunks of 6 NZW rabbits under an impervious cuff for 24 hours. Observation and scoring at 24 and 72 hours after exposure.

Results: P.I. + 2.8; no edema; well-defined erythema in 5/6 at 24 hour; 0/4 at 72 hours. 2 rabbits (male) died after 31 hours.

Classification: Core-Minimum Data; TOX Category III: CAUTION

19. Safrotin 50 EC. Primary Eye Irritation in Rabbits (Sandoz Ltd, AGRO DOK CBK 3154/78; 63/78; Sept. 29, 1978)

Test Material: Safrotin 50 EC, Batch No. 4495

0.1 ml of test material was instilled into the left eye of each of six NZW rabbits with the untreated right eye serving as a control.

The eyes were examined at 24, 48, 72 hours and 7 days, using the "Illustrated Guide for Grading Eye Irritation by Hazardous Substances". The eyes were not washed after instillation. Prior to the administration of the compound, the eyes of each rabbit were examined with UV light after instillation of a 2.0% sodium fluorescein solution.

Results: Corneal opacity in 3/6 at 24 hr; 1/6 at 48 hr. and 0/6 at 72 hr. Iritis in 2/6 at 24 hr. & 0/6 at 48 hour; Conjunctivitis in 4/6 at 24 hr. & 3/6 at 48 hr. and 0/6 at 72 hours.

Classification: Core-Minimum Data; TOX Category II: WARNING

20. Safrotin 50 EC. Diluted for Use. Primary Eye Irritation in Rabbits (Sandoz Ltd, AGRO DOK CBK 3153/78; 61/78; Sept. 29, 1978)

Test Material: Safrotin 50 EC diluted with water to a 0.2% user concentration.

0.1 ml of test material was instilled into the left eye of each of six NZW rabbits with the right eye serving as control. Observation and scoring at 24, 48, 72 hrs. and 7 days.

Results: No corneal opacity; no irritation in 6/6 rabbits.

Classification: Core-Minimum Data; TOX Category IV: CAUTION

21. Propetamphos. Primary Eye Irritation in Rabbits (Sandoz Ltd, AGRO DOK CBK 3152/78; 60/78; Sept. 29, 1978)

Test Material: propetamphos technical; purity 91.8%, Batch No. P16/17

0.1 ml of test material was instilled into the left eye of each of six NZW rabbits with the right eye serving as control. Observation and scoring at 24, 48, 72 hrs. and 7 days.

Results: No corneal opacity; no irritation in 6/6 rabbits

Classification: Core-Minimum Data; TOX Category IV: CAUTION

22. Two-Weeks Toxicity of Safrotin in Sprague-Dawley Rats when administered by inhalation (Laboratorium Fur Pharmakologie and Toxikologie, Sept. 24, 1978)

Test Material: Safrotin 50 EC

100 Sprague-Dawley rats, 157 - 165 gm for males and 138 - 154 grams for females, were divided into five groups (10 M & 10 F) consisting of control, .053 mg/L, 0.097 mg/L, 0.304 mg/L and 1.009 mg/L Safrotin.

The rats were exposed to the air/Safrotin mixture from the 1st to the 5th and from the 8th to the 12th test day (exposure time: 4 hours/animal/day). The control animals received an air-flow without Safrotin. Body weight and external appearance were observed daily. Food consumption and water intake was estimated daily.

Hematological & clinical chemistries were monitored after 2 weeks in all surviving animals.

Serum and RBC cholinesterase was determined before first administration and after 3, 7, 10, and 14 test days on all surviving animals.

Urinanalyses were done before administration and at 3, 7, 10 and 14 days of test in all surviving animals. Opthalmologic examination was performed prior to final sacrifice. Necropsy and histological examination of tissues was performed on all groups. Statistical evaluation was by analysis of variance and Student;s t-test of control and treated groups.

Results: At the lowest Safrotin concentration (0.053 mg/L) in both sexes the cholinesterase activity in serum was inhibited from the 3rd test day onwards. 0.097 mg/L safrotin caused exophthalmus, ataxia, piloerection and apathy during the second inhalation period. The body weight gain of the females was inhibited, at the end of the study significantly.

The hematological investigations showed a tendency towards a reduction of the leutocytes. At this concentration, inhibition of the cholinesterase activity in the serum was more dose-related. An increase of the RBC cholinesterase activity might be a typical effect of organophosphates preceding inhibition. The serum level of glucose in both sexes was below that of the controls, parallel to this an increase of the activity of SGPT, SGOT and SAP were noted. The macroscopic inspection showed three rats with lesions of the gastric wall. These findings were confirmed by the histological examinations.

At the safrotin concentration of 0.304 mg/L similar changes in behavior-starting earlier-were seen. The rats adopted cataleptoid - and lateral - as well as abdominal positions. Over the whole test body weight curves ran below those of untreated rats. Hematological examination showed a decrease in leucocytes and hematocrit values. In the hemogram the percentage of immature neutrophils was increased at the expense of lymphocytes.

This safrotin level caused a reduction of serum cholinesterase activity up to 65.1% (males) and 79.0% (females). The RBC cholinesterase levels, serum-glucose, SGPT, SGOT and SAP were similar to the 0.097 mg/L level. The specific gravity of the urine was higher than that of the controls.

Altogether, 12 animals died prematurely, following agonal spasms. These rats showed macro-and microscopically very often pulmonary, and in some cases gastric wall lesions. The examinations revealed partly changes in the trachea, very seldom in the nasal cavity or paranasal cavity. Most of the internal organ weights of both sexes were reduced and the adrenal of the males enlarged.

The highest safrotin - concentration (1.009 mg/L) caused the same reactions as at 0.304 mg/L level. The test level was terminated on test day 7 in view of the high mortality rate: only of males and 2 females were alive at this date.

Conclusion : Under the present test conditions the lowest concentration without changes can be expected to be below 0.053 mg safrotin/L air by inhalation. Without consideration of the decreased plasma cholinesterase, the lowest concentration without toxicity is between 0.053 mg/L and 0.097 mg/L.

23. Investigation of teratogenic potential of San 52-139 in the Rabbit (Sandoz , Inc., Pharmaceutical Research and Development; Exp.#T-1183, Oct. 17, 1978)

Test Material: San 52-139; technical propetamphos; purity 92%; Batch No. 4552

Sixty commercially obtained NZW female rabbits were used. A group of approximately 8 month old backs of the same strain and from the same supplier were used for mating. The following table presents dosages, animals used and identification of animals and dose groups.

Group	Control	Low	Mid	High
Dose (mg/kg/	0	1	4	8
day Acc.#C-78)	601 - 615	616-630	631 - 645	646 - 660
Ear Tag#*AA-)	520 - 534	535-549	550 - 564	565 - 579
Necropsy (Scheduled)				
Day of gestation	30	30	30	30
# Animals Preg.	15	15	15	15
Fetal Exam				
Total # External Exam	161	134	155	130
Total # Skeletal exam (alizarin)	111	97	110	94
Total # Visceral exam (Bouin's)	43	40	35	34

Maternal body weight was recorded on the following days of gestation: 0, 6, 10, 14, 18, 22, 26, 30. Food consumption was not recorded. Daily observations were recorded. At sacrifice on day 30 of pregnancy, examination and description of reproductive tracts and their contents, including intact and empty genital tract weights, # of corpora lutea, # conceptuses, # live, # dead, # resorptions. Selected samples of the following maternal viscera were examined and collected in formalin: liver, lungs,

trachea, kidneys, adrenals, heart, stomach and any gross lesion. Fetal examination included external, visceral and skeletal. The observation noted were divided into major, intermediate and minor levels of significance. Electronic data processing was performed on all maternal body weight data, genital tract and litter data at day 30 of gestation and fetal external, visceral and skeletal examinations.

Results: A significant body weight loss occurred in the high dose group during the treatment period while the controls, low and mid-dose showed a gain. One pregnant high dose (accession no. 660-78) died on day 15 of gestation with 11 fetuses in utero. Necropsy examination revealed tracheal and pulmonary congestion, reddish fluid in the thoracic cavity, discolored liver, and ruptured stomach. No attempt was made in this single animal to determine cause of death histologically due to the presence of extensive autolysis. No treatment-related mortality was noted in any of the groups. Necropsy examination of animals at scheduled necropsy revealed a variety of findings none of which were considered related to treatment or unusual for laboratory rabbits. No remarkable variation was seen in fertility or reproductive performance among any of the groups. No remarkable variation in the number of conceptuses was noted among groups as all average values were higher than the previous control average values.

The implantation index was also comparable to previous control values and unremarkable. Although not significantly different from controls, the average number of resorptions was slightly higher in high dose (1.4) compared to mid (0.1), low (0.8), concurrent controls and previous controls (0.5) and above the previous control maximum of 0.9. The average number of dead fetuses was comparable among the groups and previous controls. No remarkable variation in live fetuses was noted among the groups and average values were higher than the average recorded for previous controls. Overmigh survival was comparable among groups and previous control. No remarkable variation in fetal weight, dimensions and sex ratio was noted among groups, including previous controls.

External Examination

One high dose fetus (Acc.#649-1-78) was found with a cranial malformation consisting of astomia, absent nares and apparent agnathia. Died within 5 minutes. One mid dose fetus (Acc.#645-6-78) had cleft palate; visceral examination revealed intracranial hemorrhage in the area of the cerebellum. This fetus died within one hour after caesarean delivery. Cleft palate has been seen once in 904 Previous control fetuses.

One headless (acephalic) control fetus (Acc.#612-3-78) was delivered alive but died within one minute. Visceral examination was negative, but the skeletal examination revealed incomplete ossification of the first cervical vertebrae components of the first digit of both front paws and lack of ossification of the 5th sternebrae.

Another control fetus (Acc.#615-7-78) was dead, immature with eyes open, weighed only 2.5 grams and had abdominal hernia with ectopia of the liver and intestines. Because of its size and presence of severe autolysis this fetus received only an external examination and was not included in the computer generated tabulations.

Although observations of major significance were detected in treated groups, the low incidence of these malformations in the mid dose (1 fetus our of 155 examined) and high dose (1 fetus out of 130 examined) along with 2 major malformations out of 161 control fetuses does not suggest any pattern of induced teratogenic activity. External and visceral examination of intermediate and minor significant anormalies did not reveal and compound related trends.

Skeletal observation of minor, intermediate and major anomalies did not reveal any compound related trends.

Conclusion: Based on the data from this study, administration of 8 mg/kg/day to NZW rabbits resulted in a slight transitory maternal bod, weight loss in addition to a slight increase in resorption rate.

The low incidence of malformations as noted in one mid dose and one high dose fetus along with the occurrence of malformations in 2 control fetuses does not suggest any pattern of induced teratogenic activity by administrations of technical propetamphos.

Classification: Core-Minimum Data

TOX/HED:th:RD Initial WWOODROW:6/20/79