UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg.#11273-EE; Interim Reports on Propetamphos
CASWELL ~~#706A,~~ Accession#243800

FROM: William Dykstra, Toxicologist
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TO: William Miller (16)
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Recommendations:

1) The interim reports on the rat reproduction study and chronic toxicity/oncogenicity study in mice with propetamphos are acceptable as interim reports. The results of the reproduction study indicate from the data presented no consistent, dose-related significant effects at dosages up to 20 ppm (highest dose). In the chronic toxicity/oncogenicity study in mice no significant compound-induced proliferative changes have been observed. Based on submitted results, the NOEL for inhibition of cholinesterase is 0.05 mg/kg/day.

Review:

1) Propetamphos; 3-Generation Reproduction Study in Rats (Sandoz AGRO DOK CBG I. 4835/80; Report No. 55/80; August 25, 1980)

SPF Sprague-Dawley rats formed the FO-generation. The rats were between 4 and 5 weeks old at the beginning of the study. Each dose group consisted of 35 males and 35 females in the FO to F1 generation and 30 males and 30 females in the FII generation. The following dosages were used for all three generations:

K controls	-
A low	5 ppm
B mid	10 ppm
C high	20 ppm

8 pages

The animals were housed individually in Macrolon cages equiped with food cups and water bottles. The animals were allowed to have free access to food and tap water, which were available ad libitum. Propetamphos was mixed with powdered standard rat diet by means of a Turbula mixer to provide the desired dietary level. The control animals received untreated powdered standard diet. After 100 days the 35 females per group were mated with the corresponding males one by one. Each couple was kept together for 7 days. The observation of the copulatory plug was considered evidence of positive mating.

Ten pregnant females in each group were investigated for teratogenic effects. The first litter of each generation (F1A, FIIA, FIIIA) was reduced to 8 animals on day 4. They were observed for symptoms occurring between birth and day 21. Then they killed and x-rayed. Those skeletons showing abnormalities were stained and examined.

In the second litter (F1B, FIIB, FIIIB), 10 pregnant females were killed one day before giving birth by CO_2 - asphyxiation and the fetuses investigated. The skeletons were stained with Alizarin. The remaining pups served as the next generation. They were mated after 120 days as described. Brother and sister pairing was avoided. The animals of the FIIIB-generation were observed for 21 days. A breeding schematic was submitted. For the teratological part, the following specific points were investigated:

corpora lutea count
number of implantation sites
number of living and dead fetuses
number of embryonal fetuses
number of resorption sites
sex of individual fetuses
average weight of placentae
average weight of fetuses

The fetuses were dissected, eviscerated, and subjected to skeletal clearing and Alizarin staining.

In the reproduction study, the following data were collected for each litter and generation.

Identification of females and males mated.

Fertility Index (%)
Gestation Index (%)
Viability Index (%)
(4-21) Lactation Index I (%)
(14-21) Lactation Index II (%)

Average number of pups per litter, alive and stillborn, sex ratio.

Average pup weight (g) on day 1, 4, 14, 21. The individual body weights and food consumption of the mother animals were collected weekly. At the end of dietary administration, 35 animals per dose group (10 males and 25 females of the FIIIB-generation) were killed with CO_2. The appearance of the tissues was also noted in the case of macroscopic abnormalities. Samples of the following tissues were preserved in 4% formaldehyde for subsequent processing:

salivary gland	esophagus
mammary gland	stomach
skin	small/large intestines
mesenteric lymph nodes	urinary bladder
thyroids	sciatic nerve
adrenals	bone marrow (femur)
spleens	skeletal muscle
pancreas	seminal vesicle
liver	testes/ovaries
thymus	prostate/uterus
heart	eyes
lungs	optic nerve
trachea	brain
tongue	pituitary

The tissues were embedded in paraffin wax for further processing. The slides were stained with hematoxylin/eosin or Sudan .

Statistical analysis of the data was performed.

Results:

Summarized results up to FIIIA generation were presented. In the pups alive, the mid- and high-dose of the FIA generation had significantly lower numbers than the control.

All treated groups of the FIIB generation showed significantly higher results in pups alive. The number of stillborn pups was significantly higher at 10 ppm of the FIB generation. Pup body weight on day 1 was significantly lower only in the FIIB generation of all treated groups. On day 4, in the 20 ppm dosage group of the FIIA and the 5 and 10 ppm dosage group of the FIIB-generation, the pup body weight was lower than in the controls. At 14 days and 21 days, no dose-related differences were observed.

The fertility figures showed lower values in the FIA generation (groups B and C), in the FIB generation (all treated groups) and in the FIIIA generation (group C). Higher values were seen in the FIIB generation (all groups). None of the fertility differences were significant. The lactation Index showed differences in the FIIB generation in group A and B (lower figures) and in the FIB-generation (higher figures) in group A and B. None of the lactation I index differences were significant.

Conclusion:

No consistent, dose-related significant effects were observed at dosages up to 20 ppm in the interim report of the reproduction study.

Classification: Supplementary Data

(a) Interim Report

2. Interim 18-Month Report on Lifetime Oral (Diet) Toxicity/Carcinogenicity Study in the Mouse on San 52-139 (Sandoz Project T-1220; WIL#79218; November 19, 1980)

To assess the potential chronic toxicity and carcinogenicity of SAN 52-139, eight hundred (800) weanling Charles River CD-1 mice were randomly divided into six groups and administered SAN 52-139 by diet at dose levels indicated:

Group mg/kg/day	Number of mice/sex
Control I	80
Control II	80
0.05	10
1	80
6	70
21	80

The pretest week-1 females weighed approximately 16 to 17 grams and males approximately 19 to 20 grams. Animals are fed Purina Lab Chow (certified) and water ad libitum. All animals are housed in individual stainless steel wire botton cages in a laminar air-flow (Bio-Clean System) air conditioned room. WIL Research Laboratories, located in Cincinnati, Ohio, is conducting the antemortem phase of the study.

On receival of the test animals into test facilities, the animals were allowed to acclimate one week prior to initiation of pretest week-1. Pretest week-1 started February 13, 1979. A 12 and 18 month interim sacrifice was performed on February 13 & 14, and August 13 & 14, 1980, respectively. Termination of the study is scheduled for November 17 through 19, 1980 (92 weeks of test compound administration). Batch/Lot No. 1677 (91.8% purity) of technical grade SAN 52-139 in a liquid state is being used throughout the duration of the study. Diet concentrations are adjusted for each group/sex based on the most recent body weight and food consumption data obtained.

All animals on study are examined once daily and observations recorded. Individual body weight of all animals on study, and food consumption of 25 animals per sex per group, are taken on a weekly basis starting in pretest week-1 through test week-13, and every other week thereafter to termination of the study. Palpation of masses of all animals on study, excluding animals placed on study for cholinesterase determinations, are routinely performed weekly through termination of the study.

Hematologic examinations are performed in weeks 25, 51, 77 and 91 on males and 10 females from all groups, excluding group III, 0.05 mg/kg/day dose level. Animals are bled from the retro-orbital sinus for the following hematological determinations: hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet and reticulocyte counts.

Routinely, the animals selected for 12 and 18 month interim necropsies are the same animals evaluated clinicopathologically at bleeding intervals which precede the necropsy. Biochemical examinations are performed in weeks 26, 52, 78 and 92 on 10 males and 10 females from all groups, excluding group III, 0.05 mg/kg/day dose level. Animals are fasted approximately 4 to 5 hours prior to bleeding from the retro-orbital sinus for the following determinations: glucose, BUN, SAP, SGOT, SGPT and total protein. The same animals evaluated for biochemical changes have been evaluated hematologically in the previous

week of the study. The animals sacrificed at interim 12 and 18 month necropsies are routinely the same animals evaluated clinicopathologically in preceding weeks. Plasma and RBC cholinesterase levels are evaluated in 10 males and 10 females from all groups on study in pretest week-1 and weeks 2, 6, 12, 24, 50, 77 and 87. The surviving animals from each group of 10 males and 10 females placed on study only for cholinesterase monitoring will have liver and brain cholinesterase levels determined at terminal necropsy.

Blood samples are obtained from the retro-orbital sinus. All animals on study, excluding 10 males and 10 females placed on study for cholinesterase monitoring, will have a complete necropsy and histopathological examination performed on the following tissues:

gross lesions - all tissues
tissue masses or suspect tumors
adrenals
aorta
bone
cecum
colon
esophagus
eyes
gonads
heart
kidneys
liver
lungs and mainstem bronchi
lymph nodes
axillary
mandibular
mesenteric
respiratory
blood smear
bone marrow
brain (3 sections)
head
mammary gland
muscle, skeletal
pancreas
parathyroids
pituitary
prostate
salivary gland
sciatic nerve
skin
small intestine
spinal cord
spleen
stomach
trachea
ureters
urinary bladder
uterus
vagina

An interim necropsy in months 12 and 18 was performed on 10 males and 10 females per group (excludes group III, 0.05 mg/kg/day). In week 93 all surviving animals on study will be necropsied and examined histopathologically.

Results:

No significant compound induced toxic effects have been observed through week 78.

Throughout the duration of the study, a sporadic incidence among all groups including controls of enlargement of the testes has been observed. Through week 78, no significant histopathological fidnings have been observed in the testes of animals sacrified or found dead, which previously were noted with enlargement of the testes.

No significant compound-induced effects on mortality have been observed through week 79. The greatest mortality has been observed at the female high dose level (21 mg/kg/day), which shows a survival incidence of 26/50 animals (52% survival).

Excluding animals placed on study for interim sacrifice or cholinesterase determinations, the survivability of all control and treated groups is greater than 50% at week 79.

No significant compound-induced change in body weight gain have been observed through week 79. Sporadic statistically significant increases or decreases in mean body weight have been observed through week 79. However, no consistent decrease or increase has been observed and these changes are not considered to be of toxicological significance.

A compound-induced decrease in food consumption at the high dose level for both males and females has routinely been observed through week 79. A possible compound effect has also been observed at both the low and middle dose levels. The decrease in food consumption observed at all dose levels approximates a 10% reduction compared to the pooled controls (I and II). No significant effect on body weight has been observed and the intended dose levels to be administered have been approximated throughout the study.

No significant compound-induced effects in hematology or clinical chemistries have been observed through week 78.

A significant dose-related compound induced inhibition of both plasma and RBC cholinesterase activity has been observed at the 6 and 21 mg/kg/day dose levels. A significant inhibition of plasma cholinesterase activity has also been observed in the male only at 1 mg/kg/day dose level. The NOEL for inhibition of plasma and RBC cholinesterase is 0.05 mg/kg/day. RBC cholinesterase was inhibited at 1.0 mg/kg/day, but not significantly.

No significant compound-induced gross changes have been observed either at the 12 or 18 month interim necropsies or in spontaneous deaths of animals on study through week 79.

At 18 months diffferences in testes, heart and kidney absolute or relative organ weights at the 21 mg/kg/day dose level were observed. Although the testes relative to body weight increased in comparison to control I, no differendce between control II was apparent. A slight decrease in absolute heart weight was observed in females at the 21 mg/kg/day dose level. However, no significnat histopathological changes were observed in the animals sacrificed in the 12 month interim sacrifice. A slight decrease in mean absolute kidney weight was observed at the 18 month interim necropsy at the male 21 mg/kg/day dose level.

No treatment related proliferative and/or non-proliferative changes have been observed through the 12 month interim sacrifice. Histopathological examination of the 18-month interim sacrifice has not been performed.

Conclusion:

The results of the interim report indicate the NOEL for cholinesterase inhibition is 0.05 mg/kg/day. No treatment related proliferative and/or non-proliferative changes have been observed through the 12 month interim sacrifice.

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