UNITE ɔT .ES ENVIRONMENTAL PROTEC ɔN GENCY

DATE: APR 29 1980

SUBJECT: EPA Reg.#11273-EE; 11273-ER; Delayed Neurotoxicity Study in Chickens on San 52-139.
CASWELL#706A Accession#232185

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Recommendations:

1) For the label of Safrotin EC (11273-EE), the words "Keep Out of Reach of Children" should appear on the label. The correct label signal word is considered to be "Warning" rather "Danger".

2) San 52-139 was not a delayed neurotoxic agent in the delayed neurotoxicity study in chickens. The study is acceptable as Core-Minimum Data.

3) The submitted toxicology studies support the registration of Propetamphos (11273-ER) and the conditional registration of Safrotin 4 EC (11273-EE). For registration of Safrotin 4 EC, the following studies are needed on the technical:

   a) reproduction - 1 species
   b) chronic/oncogenic - 1 species
   c) Residue data on food from home use or food-handling establishments.

Review:

1) Acute Delayed Neurotoxicity Study in the Chickens on San 52-139; (Sandoz Project T-1447; Bio/dynamics No. 6182-79).

1) LD_{50} of San 52-139

Twenty-eight (28) adult healthy hens were randomly divided into seven groups of four birds each and administered the following dose levels of San 52-139 in PEG-400: 57.9, 80.7, 111.9, 155.7, 216.3, and 300 mg/kg; the seventh group was administered 750 mg/kg of TOCP (tri-o-cresylphosphate). All birds were fasted overnight approximately 16 hours prior to administration of San 52-139 and TOCP, both in the acute LD_{50} and acute delayed neurotoxicity studies.

Body weights and observations of neurotoxicologic signs were routinely recorded and the surviving birds were necropsied.

Results: The calculated oral LD_{50} of San 52-139 is 78 mg/kg, with 95% confidence limits of 48 to 108 mg/kg.

Toxic Signs: TOCP birds were observed to exhibit classical delayed neurotoxicity, consisting of leg weakness and progressive ataxia.

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2) Neurotoxicity Study

Thirty (30) additional adult birds were randomly divided into three groups of ten birds each and administered at a volume of 2 ml/kg the following:

PEG-400 (negative control), San 52-139 at a dose level of 200 mg/kg, and TOCP at a dose level of 750 mg/kg.

Prior to initial dosing of SAN 52-139 in the acute delayed neurotoxicity study, an antidotal regimen of 10 to 20 mg/kg of atropine S.C. and 2-PAM i.m. were administered from 15 minutes to 48 hours post-treatment with SAN 52-139. The route of administration and dose of antidote was varied specifically on an individual animal basis when necessary.

Food consumption estimates and body weights were routinely taken, and daily observations were made throughout the duration of the study. Since no overt delayed neurotoxologic signs were observed in the San 52-139 birds 21 days post-treatment, all San 52-139 birds were again administered 200 mg/kg orally via intubation, and a similar antidotal regimen was employed in Test Days 22 and 23.

Results

Hens that received TOCP showed no acute effects. Progressive leg weakness, incoordination, ataxia and paralysis commenced 10-15 days and culminated in sacrifice in extremis 12-24 days after dosing. One hen (number 25) died on Day 6 without showing any ante-mortem signs.

Transient body weight losses occurred after dosing in San 52-139 treated hens but the body weights in the second and third weeks after dosing were essentially normal. Positive and vehicle controls did not show any deviation from normality in respect of body weights.

Typical nicotinic and muscarinic signs were seen in San 52-139 treated birds for up to 48 hours after each dose thereafter the hens showed no signs of residual or delayed toxicity and thus indicated no potential to cause delayed nuerotoxicity. No deaths occurred. Vehicle control hens remained essentially normal throughout the study.

After 42 days on test, all vehicle (negative) control (PEG-400) and San 52-139 birds survived and were sacrificed on Test Day 43. All TOCP birds had previously been sacrificed in extremis by Test Day 24 of the study. It should be noted that "forced exercise" was performed routinely on all birds throughout the duration of the study.

A necropsy was performed on all test birds and brain, spinal cord, and sciatic nerve fixed in 10% neutral buffered formalin. All spinal cords and sciatic nerve were processed by Sandoz, Inc. and duplicate sections stained with H&E and Hematoxylin and Luxol Fast Blue.

The incidence of neurotoxic lesions observed in the spinal cord and peripheral nerves was as follows:

0/10 of the negative control; 9/10 of the TOCP treated birds; and 0/10 of the San 52-139 treated birds.

Conclusion: San 52-139 was not a delayed neurotoxic agent in this study.

Classification: Core-Minimum Data

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