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

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DEC 1 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No.: 432-667. SCOURGE Insecticide with SBP-1382 (resmethrin)/piperonyl butoxide MF Formula II and PP#9F2209, Resmethrin: exemption from a tolerance associated with use to control mosquitoes in feedlots, cropland, pastures and rangeland.

TOX CHEM No.: 83E (resmethrin)
670 (piperonyl butoxide)
TOX PROJECT No.: 9-2177
Record No.: 251951

FROM: John Doherty John Doherty 10/20/89
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: Phil Hutton
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THROUGH: Roger Gardner
Acting Section Head
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Background

The Roussel Bio Corporation (Englewood Cliffs, New Jersey) is requesting an exemption from a tolerance be granted related to the use of resmethrin to control mosquitoes in feedlots, croplands, pastures and rangeland. In support of this exemption from a tolerance the registrant has submitted an acute inhalation toxicity study with rats and a dermal sensitization with guinea pigs with the product SCOURGE Insecticide (18% resmethrin and 54% piperonyl butoxide). No other data were submitted with this action but additional studies were submitted with HED Project No. 9-2179 and were reviewed separately (date of memo pending).

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Toxicology Branch I (TB-I) has reviewed the inhalation and sensitization studies (refer to DERs attached). The following comments have been prepared by TB-I to address the registration of SCOURGE Insecticide and PP# 9F2209.

Toxicology Branch Comments

A. PP#9F2209.

1. The RfD/ADI document outlining the toxicity data base used in setting the ADI for resmethrin is attached. The data gaps for resmethrin are acute oral and dermal toxicity, subchronic (21-day) dermal toxicity, mutagenicity and genetic toxicity (a study from each of the three categories) and general metabolism and pharmacokinetics.

With regard to piperonyl butoxide, the RfD/ADI committee has not completed its review to assign an RfD for this chemical. A package has been prepared and the rat chronic feeding/carcinogenicity study with a NOEL < 30 mg/kg/day and not demonstrating evidence of carcinogenicity has been recommended for the RfD. Since there was no definite NOEL (although only liver weight increases were noted in the low dose (30 mg/kg/day) females), a modifying factor may be used together with the traditional 100 fold safety factor to calculate the Acceptable Daily Intake (ADI).

Additional data available (studies determined to be acceptable by current standards) to support tolerances or exemptions from tolerances for piperonyl butoxide are a rabbit developmental toxicity study (NOEL for developmental toxicity = 200 mg/kg/day (HDT), NOEL for maternal toxicity = 50 mg/kg/day, LEL = 100 mg/kg/day, decrease in body weight. A multi generation reproduction study with a NOEL of 1000 ppm and a LEL of 5000 ppm (decreases in weight gain).

The data gaps for piperonyl butoxide are acute oral and dermal toxicity, subchronic (21-day) dermal toxicity, subchronic and chronic feeding (dog), carcinogenicity (mouse), developmental toxicity (second species, i.e. rat), mutagenicity (a study from category 1 (gene mutations) and 3 (other mechanism), general metabolism and pharmacokinetics.

2. The decision to grant an exemption from a tolerance is made largely on the basis of the expected residues in edible foodstuffs together with the known toxicity of the pesticides. In this regard, if Dietary Exposure Branch determines that the residues of either resmethrin and piperonyl butoxide in foodstuffs including secondary residues in meat, meat products and milk and dairy products are negligible and will not impact on the ADI, TB-I has no objections to granting an exemption from a requirement for a tolerance. If residues in foodstuffs will be

significant, than the impact of these residues on the ADI will have to be assessed by Science Analysis and Coordination Branch. If the effect of the residues on the ADI results in an increase which TB-I deems significant, than at least some of the data gaps indicated above for these pesticide may have to be completed depending on the magnitude of the impact on the ADI.

B. Registration of the product SCOURGE Insecticide.

1. The dermal sensitization study with guinea pigs was determined to be an ACCEPTABLE study and the product was not demonstrated to be a sensitizer.

2. The acute inhalation study was reviewed and determined to be UNACCEPTABLE. The problems with this study relate to the design of the exposure test chamber which, in the absence of a demonstration otherwise, TB-I does not consider will result in uniform distribution of the test atmosphere. Future studies using this chamber should not be presented to the Agency unless it is documented that the chamber atmosphere was constantly uniform throughout the chamber. Also studies conducted after August 1989 are expected to have 25% of the particles of < 1 micrometer in diameter. No Quality Assurance Statement was provided with the study and such statements have bee required since 1983.

The study, however, did not indicate that the product tested was of a high order of toxicity by the inhalation route. For example there were no deaths and only transient symptoms at an estimated exposure level of > 5 mg/l (criteria for toxicity Category IV). Based on the known toxicity of resmethrin and piperonyl butoxide, a low order of toxicity (category III or IV) would reasonably be expected for this product. For example, the acute oral LD_{50} for this product is 2700 (2000-3600) mg/kg for combined sexes (Toxicity Category III, Hutton review, see point 2 below). Thus, TB-I does not consider it necessary to repeat an acute inhalation toxicity study with this product.

2. The label currently has the signal word CAUTION. The acute toxicity studies supporting the label were reviewed by Registration Division (refer to P. Hutton review dated October 4, 1983). Thus, TB-I cannot confirm the appropriateness of the signal word or precautionary statements.

3. TB-I notes, however, that the product contains "aromatic petroleum solvent". Such ingredients are supposed to be defined on the label of pesticide products.

Reviewed by: John Doherty 11-22-89
Section I, Toxicology Branch I (H7509C)
Secondary reviewer: John Whalen JW 11-22-89
Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-3. Acute inhalation toxicity -rats

MRID NO.: 406958-03 TOX. CHEM. NO.: 83E

TEST MATERIAL: SBP-1382 Piperonyl butoxide Formula II)
(18% resmethrin and 54% piperonyl butoxide)
EPA Reg. No. 432-667.

TEST ANIMALS: Male and female young adult Sprague-Dawley rats
Ace Animals Inc., Boyertown, Pa. 19512.

STUDY NUMBER(S): #MB 84-7131

SPONSOR: Penick Corp., Submitted by Roussel Bio Corp.

TESTING FACILITY: Dept. Physiology/Biophysics, Temple University
School of Dentistry.

TITLE OF REPORT: "Inhalation Toxicity Report in Compound SBP-1382
Piperonyl butoxide (Formula II)"

AUTHOR: Martin F. Tansey. Ph.D.

REPORT ISSUED: June 14, 1984

CONCLUSIONS:

LC_{50} estimated to > 5.20 $\pm$ 1.03 mg/l (4 hours). Only dose tested. No deaths, signs of transient tremors and irritation. Necropsy was unremarkable. Not assigned to toxicity categry because study is UNACCEPTABLE.

Classification: UNACCEPTABLE [Chamber design may not allow uniform distribution of test atmosphere, particle size of atmosphere less than recommended size. No Quality Assurance Statement provided.]

Special Review Criteria (40 CFR 154.7) N/A.

Quality Assurance Statement: None provided.

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Review

In this study a single group of test Sprague-Dawley rats (5 males and 5 females, young adult but age not specified, approximately 175-225 gms) were exposed to an atmosphere containing "5 mg/l" nominal concentration of SBP-1382 Piperonyl butoxide (Formula II) for a period of 4 hours. Following exposure the rats were observed for reactions for 14 days.

The exposure chamber consisted of a 57 liter glass chamber. Within the chamber, the rats were separated by wire screening. Generation of the aerosol was by means of a Harvard infusion pump and syringe which metered the test material into atomizing nozzle for eventual mixing with air. After entering the exposure chamber from a port on the side, the test atmosphere was drawn over the test animals and out of the chamber through an exhaust valve at the bottom of the chamber. The design of this test chamber is considered questionable by TB-I. For example, the test atmosphere enters from the side and exits from the bottom, but there is no assurance that the test atmosphere is uniform throughout the test chamber.

The chamber atmospheric concentration was determined by taking a sample by means of an exhaust tube from an area near the top center of the chamber. In the absence of evidence otherwise, TB-I assumes that the same area of the test chamber was analyzed each time, further calling into question whether or not the test atmosphere was uniform. The chamber air was drawn through a glass impinger containing acetone by means of a vacuum pump (2 liters/min). The acetone trapping solution was analyzed in accordance with the Penick Company's analytical method. The mean analytical concentration was determined to be 5.20 $\pm$ 1.03 mg/l based on 8 determinations (range 4.07-7.40). The chamber concentrations were expressed as mg/l of "SBP-1382 Piperonyl Butoxide (Formula II)". The chamber atmosphere was analyzed for resmethrin, thus, the chamber concentrations must have been extrapolated from the concentration of resmethrin determined by analysis.

The particle size of the test atmosphere was determined by means of an Anderson Cascade Impactor. The mass median diameter ranged from 2.48 to 2.65 um and the geometric standard deviation ranged from 1.80 to 2.13. Of the eight determinations made, the range for percentage of particles < 1.1 um in diameter was 1.4 to 4.2 percent. This is considerably below the recommended 25%. Approximately 35% of the particles were assessed to be less than 3.3 micrometers.

Results.

None of the rats died, only signs of tremors (one male and 2 females), irritation (ocular) and preening were apparent. The rats gained weight following exposure and necropsy was unremarkable.

CONCLUSION. This study is UNACCEPTABLE. The problems with this study relate to chamber design which TB-I does not consider would result in uniform distribution of the test material in the atmosphere. This type of chamber should not be used in future studies unless it is demonstrated that uniform chamber atmospheres of the test material are constantly generated. All inhalation toxicity studies conducted after the publication Hazard Evaluation Standard Evaluation Procedure (EPA-540/09-88-101, August, 1988) are expected to have 25% of the particles of less than 1 um in diameter. The study did not have a Quality Assurance Statement and such statements are required for studies performed after Dec. 29, 1983.

Reviewed by: John Doherty John Doherty 10/23/89
Section I, Toxicology Branch I (H7509C)
Secondary reviewer: Roger Gardner
Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-6. Delayed contact sensitivity-guinea pigs.

MRID NO.: 406958-05 TOX. CHEM. NO.: 83E

TEST MATERIAL: Scourge Insecticide with SBP-1382/Piperonyl Butoxide [18% and 54% MF Formula II]

TEST ANIMALS: Female albino guinea pigs, Harltey/Dunkin strain. D. Hall, Newchurch, Staffordshire, England.

STUDY NUMBER(S): HRC Report No.: 84935 D/SBP 10/SS

SPONSOR: Penick Corporation. Submitter by Roussel Bio Corp.

TESTING FACILITY: Huntingdon Research center, Huntingdon, England.

TITLE OF REPORT: SCOURGE Insecticide with SBP-1382/Piperonyl Butoxide [18% and 54% MF Formula II]

AUTHOR: Jennifer A. Seaber

REPORT ISSUED: February 24, 1988

CONCLUSIONS:

The product SCOURGE Insecticide was <u>not</u> demonstrated to be a sensitizer in this study.

Classification: CORE GUIDELINE

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement: A statement signed by K.W.G. Shillam, Director of Quality Assurance attested that the <u>procedures</u> used for this type of study are periodically inspected. The in-life phase of this particular study was apparently not specifically inspected but the study report was audited and found to be an accurate presentation of the data.

REVIEW

In this study two groups of guinea pigs (females), one of 20 (test group) and the other of 10 (control group) were

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subjected to s dermal sensitization study based on the method of Buehler (Arch. Dermatol. 91:171(1965). No positive control group was included.

The test report states that a preliminary investigation determined the irritant properties of SCOURGE such that "slightly irritant" and "non-irritant" concentrations were selected for the induction and challenge phases of the study respectively. No data on this preliminary experiment were presented. The dosing levels selected were the test material as supplied (undiluted SCOURGE) and 75% (diluted with liquid paraffin) concentration.

Induction phase.

The skin of the left shoulder blade was prepared by clipping free of hair. A 2 x 2 cm patch of surgical gauze was saturated with 0.5 ml of SCOURGE and applied to the skin and kept in place with bandages. Contact of the test material was for 6 hours before removal. Irritation was assessed after 24 hours. Nine induction applications were made, three times a week during a three week period. The control animals were bandaged similarly but without test material

Challlenge phase.

Two weeks after the last induction application a sample of 75% SCOURGE was applied to the right flank (prepared by removing hair). It was not specifically stated but it was implied that the challenge application was kept in place for 6 hours. The challenge site was evaluated 24, 48 an 72 hours after removal of the test material.

Results

There were signs of slight irritancy due to the test material when applied during the induction phase. These included erythema (maximum score 2) and edema (maximum score 1) there was also occasional dryness and thickening and sloughing. The control animals also had erythema (maximum score 1.1) but no edema.

Following the challenge application, several of the guinea pigs had erythema (maximum score 1.1) but none had edema. Therefore the irritation following the challenge dose did not exceed the induction irritation. The study did not demonstrate that SCOURGE was a sensitzer based on these data.

CONCLUSION. This study is ACCEPTABLE. SCOURGE was not demonstrated to be a sensitizer in this study.