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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No.: 432-487. Resmethrin: Review of a 90-day subchronic inhalation study in rats conducted by the Huntingdon Research Centre, England and dated June 26, 1985.

TOX CHEM No.: 83E
TOX PROJECT No.: 8-0855
Record No.: 221237

FROM: John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Phil Hutton
Product Manager #17
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

The S. B. Penick Co. has submitted a 90-day subchronic inhalation study in response to an earlier request from Toxicology Branch (TB, refer to E. R. Budd memo dated June 15, 1982 for EPA Reg. No.: 432-457) to support indoor uses of this insecticide and its formulations.

TB has reviewed the study (refer to Data Evaluation Record attached) and the following comments apply.

Toxicology Branch Comments.

1. The study has been classified as CORE GUIDELINES and fulfills the requirement for a subchronic inhalation study in rats.

2. TB's conclusions include that no NOEL has been established for behavioral reactions. In particular, the study report

describes symptoms occurring at the lowest test dose level (0.1 mg/l). Although these reactions were not noted until during exposure 27 (approximately one-third of the way through the study) at the low dose, these same symptoms were reported as being present at an earlier time of onset (10th exposure) and of increased intensity at the next higher dose level (0.3 mg/l).

3. The study also did not demonstrate a NOEL for decreased blood glucose levels in males. A similar effect of resmethrin on blood glucose levels was, however, not also observed in the rat chronic feeding study.

4. In females, no NOEL was established for body weight gain which was reduced in the first four weeks of the study and serum urea levels were increased at week 12 for the low dose group.

5. Although no NOEL has been established by these data, TB is not requiring a second study to establish the NOEL. Since only minimal effects were observed at the lowest dosage level tested of 0.1 mg/l, no useful scientific or regulatory purpose would be served by requiring the study to be repeated at lower dosage levels.

Study Reviewed

Study	Result	Classification
82-4. 90-day sub-chronic inhalation-rats. Huntingdon Research Centre, England, Study No. SBP 6/84997, June 26, 1985.	NOEL < 0.1 mg/l. See review for details.	GUIDELINES

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Reviewed By: J.D. Doherty
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: 82-4. 90-Day Subchronic Inhalation-Rats

TOX Chem. No.: 83E

Accession No.: Not provided.*

MRID No.: 158476

Test Material: Technical Grade Resmethrin (Batch No. 3521-LFV-37-LF-695)

Synonyms: SBP-1382

Study Nos.: SBP 6/84997

Sponsor: S.B. Penick Company

Testing Facility: Huntingdon Research Centre, England

Title of Report: Resmethrin (SBP-1382 Technical) 90-Day Inhalation Toxicity Study in the Rat.

Author(s): Coombs, D.W.; Hardy, C.J.; Clark, G.C.; Street, A.E.; Gopinah, C.; Lewis, D.J.; Rao, R.S.

Report Issued: June 26, 1985

Conclusions:

NOEL < 0.1 mg/L - At this level, signs of "sneezing" and "agitated grooming" were evident during exposure 27 and apparently afterwards. Glucose levels decreased in males. Females showed a decrease (-13%) in body weight gain during weeks 1-4 and an increase in serum urea (32%) at week 12.

At 0.3 mg/L - These symptoms intensified and started at exposure 10 and other clinical signs were evident which included "rubbing the paws on the face," "adoption of a prone posture," and "red staining of the snout." Glucose levels decreased in males and females. Female body weight gain was decreased during weeks 1-4. Serum levels of urea were elevated in males at week 5 and females at week 12.

At 1.0 mg/L - These same symptoms were evident as were other signs of irritation to the atmosphere including decreased locomotor activity and grooming activity, tremors (when handled),

* As per Mike Hendershot the Acc No is 262536

convulsions (one male and two females), and single incidences of extensor thrust abolished and of vocalization. Decreased weight gain in males and females. Decreased blood glucose levels and elevated albumin/globulin ratio. Possible decrease in blood levels of Na^{+} and Ca^{++}. Increased liver weight, generalized lymphocyte enlargement, and "minimal increase in follicular height" of the thyroid. Thyroid, testis and uterus showed in-increased organ weights. Serum levels of urea were elevated for males at week 5 and 12 and for females at week 12.

Classification: Although a NOEL was not established in this study (minimal effects were observed at the lowest dosage level tested of 0.1 mg/l) no useful scientific or regulatory purpose would be served by requiring the study to be repeated at lower dosage levels. This study is classified as CORE GUIDELINES and fulfills the requirement for a subchronic inhalation study in rats.

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

Quality Assurance Statement:

A statement signed by K.W.G. Shilliam (dated June 24, 1985) attested that five inspections were made and seven reports provided including the final report.

Review:

A. Experimental - The test material (technical grade resmethrin, Batch No. 3521-LFV-37-LF-695, purity not stated) was generated into the test chamber (especially designed for inhalation studies) by first heating the crystalline solid to 70 degrees C, putting the liquified chemical into syringes, and attaching the syringes to infusion pumps. The syringes were kept warm to prevent the recrystallization of the resmethrin by use of a coiled tube wrapped around the syringe through which water at 70 degrees C was passed. The infusion pumps were adjusted to deliver a specified volume which was mixed with air and forced into the exposure chamber. Each chamber had air sampling ports such that the air could be sampled to assure a uniform distribution of the aerosolized resmethrin. The air was sampled to assess for resmethrin concentration by withdrawing 5, 10, or 30 liters of air through a glass fiber filter (Whatman GP/A, 3.7 cm diameter). The filters were then transferred to extraction tubes and extracted with acetone for analysis by gas chromatography.

Gas chromatographic analysis of the material extracted from the filters indicated that the six sampling ports showed a uniform distribution of resmethrin within the chamber and the atmospheric concentration as indicated and compared with the nominal concentrations is shown in the following table.

Group	Resmethrin Concentration (g/m^3)		
	Target	Analyzed	Nominal
2	0.1	0.1	0.35
3	0.3	0.3	0.93
4	1.0	1.16	3.51

There was a threefold difference in atmospheric concentrations when the nominal concentration was compared with the analyzed level. The study report maintains that this difference is due to losses of resmethrin by crystallization on the walls of the elutriation column and ductwork leading to the exposure chamber.

TB notes that the assumption of crystallization of resmethrin was not supported by data. The question arises as to whether or not the filtration method used was a valid quantitative method for assessing the chamber atmosphere. For example, was the filter used to trap the resmethrin (Whatman GP/A) 100 percent efficient? If not, the chamber atmosphere could have been higher than indicated by the analysis presented.

The test atmosphere was also assessed for particle size distribution using a May Multistage Liquid Impinger. For each of the three exposure groups, -> 93.7 percent (mean) of the particles were reported as being less than 5.5 um in aerodynamic diameter.

The test animals used were Wistar (Crl:COBS(WI)Br) strain and were obtained from Charles River UK Kent, England. They were young adults 6 to 7 weeks old on receipt. Each dose group including the control group consisted of 16 males and 16 females, except that the high-dose group included 10 of each sex extra which were allowed to recover for 4 weeks following the last exposure. Exposure was by whole body, for 6 hours a day, 5 days a week over a period of 13 weeks or 90 days.

[Note: The target dose levels were set as a result of a preliminary dose range-finding study which indicated that rats exposed to 3 g/m^3 had whole body tremors and were hypersensitive to touch. During exposure these rats had excessive salivation, and lost weight or gained less weight than the controls. Some signs as above were also noted in some of the rats exposed to 1 g/m^3.]

B. Results (Main Study)

1. Clinical Signs - Some signs of reaction during exposure were noted at all dose levels. In the low-dose group (0.1 mg/L)

the rats were reported as "sneezing" and displayed "agitated grooming" which were reported as first being noted during exposure 27 (approximately one third of the way through the study).

Signs of reaction in the mid-dose group (0.3 mg/L) were first reported during exposure 10. In addition to the symptoms at the lower dose there were reports of "rubbing the paws on the face," "adoption of a prone posture," and "red staining of the snout."

Signs of reaction in the high-dose group (1.0 mg/L) were reported from the first exposure onwards. In addition to the symptoms at the lower dose levels there were reports of "rubbing the chin on the grid of the floor of the exposure cage," "eyes partially or completely shut," "licking of the inside of the mouth," "occasional twitching," and "evidence of slight salivation indicated by dried fur under the chin."

2. Special Neurobehavioral Assessment - The rats (4 of each sex for the controls and 8 of each sex for each group of rats exposed to resmethrin) were subjected to a "systematic assessment of the behavioral and physiological states" on 8 occasions (preexposure, postexposure days 1, 2, 4, and 7, and postexposure during weeks 4, 8, and 13). This assessment included observation of (while the rats were in the cages) locomotor activity, stereotyped behavior, tremors, twitches, convulsions, abnormal body carriage, abnormal gait, position of tail, piloerection, and respiration. The rats were handled and observed for vocalization, body tone, skin color, cyanosis, lacrimation, salivation, righting reflex, pinna reflexes, corneal reflexes, pain response, and extensor thrust. Grooming behavior and ptosis were also monitored.

No effects were reported in the low-dose exposure group at any time.

The only effects reported in the mid-dose group were at week 13. Two rats (a male and a female) were reported as salivating.

Some signs were reported in the high-dose group in the early days of exposure. These included decreased locomotor activity and grooming activity, tremors (when handled), convulsions (three rats, one male and two females), extensor thrust abolished (one rat), and vocalization (one rat).

On this basis, a NOEL can be assigned as 0.3 mg/m^3. The

two incidences of salivation at 13 weeks in this group are not considered sufficient to be a definite effect of resmethrin exposure.

3. Mortality - Two rats (a male at week 5 and a female at week 13) in the high-dose group were sacrificed because of poor general physical condition including weight loss.

4. Body Weight Gain and Food and Water Consumption - During the first 4 weeks, the high-dose group males gained less weight (-16%) than the controls. This decrease was statistically significant ($p < .05$ using William's test). During this same time interval all female exposed groups gained less weight than the controls. The low- and mid-dose groups gained 13 percent less and the high-dose group gained 22 percent less than the control. All decreases were statistically significant.

   Food consumption data showed that the female high-dose test group consumed less feed than the control (-9% during the first stage of the study, or up to week 4). The high-dose female group was also noted to consume slightly more water (+14%) during weeks 3 to 5.

5. Rectal Temperature - Readings of the body temperature of the rats (4 of each sex for the controls, eight of each sex for the treated groups) were made eight times during the course of the study by inserting a probe into the rectum. No effects attributable to the exposure to resmethrin were reported.

6. Ophthalmoscopy - The eyes of 10 male and 10 female rats from the control and high-dose groups were examined prior to the start of exposure and during the final week of exposure using an indirect ophthalmoscope. No treatment-related effects were reported.

7. Hematology - Blood was collected before exposure and at weeks 5 and 12 of exposure. The following checked items were assessed.

	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differential count
X	Leukocyte count (WBC)		Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HBC conc. (MCHC)
	Platelet count	X	Mean corpuscular volume (MCV)
		X	Packed cell volume
		X	Cell morphology

The variations from the norm or control group that were determined to be statistically significantly different included reduced (different by 10%) MCV for females in the high-dose group at 5 weeks, and at 12 weeks (6%). Among the males, MCHC was elevated for all groups at 12 weeks (3 to 7%), but no dose-dependent effect was noted. MCV was also decreased for males at 12 weeks for the mid (-10%) and high (-2%). Among the white blood cell parameters measured, several differences were noted among the female groups. These included total count (-29% for the low, -36% for the mid, and -32% for the high). Neutrophil and lymphocyte counts were also down to account for the total count being low.

The study report asserts that the magnitude and lack of definite dose-dependent changes indicate that these apparent discrepancies in blood counts are not related to the toxicity of resmethrin.

8. Clinical Chemistry - The blood was withdrawn from the rats at week 5 and week 12 of exposure. The following checked parameters were investigated.

	Electrolytes:		Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorous	X	Cholesterol
X	Potassium	X	Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase	X	Total protein

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Enzymes (cont'd)
Cholinesterase
Creatinine phosphokinase
Lactic acid dehydrogenase
X Serum alanine aminotransferase (also SGPT)
X Serum aspartate aminotransferase (also SGOT)

Other (cont'd)
Triglycerides
Albumin/Globulin ratio

Results:

[Note: Tables 13 and 14 from the study report are attached to present the results of analysis].

Of these parameters, glucose values were generally lower (13 to 29% for males and 23% for females at week 5 and 21 to 28% for males and 21 to 26% for females at week 12). The low dose group males were 13 percent lower at week 5. The glucose levels for the animals in the recovery group were higher than the week 12 assessments, but since there was no control group to compare the values with it could not be determined if the glucose level was still affected. The test laboratory considered that the decreases in glucose levels were a result of exposure to resmethrin.

The albumin/globulin ratio for the high-dose group (+14% and +15% for males, +15% and +23% for females at weeks 5 and 12) were also considered to be elevated due to resmethrin exposure.

The urea levels were also elevated in males for the mid (40%) and high (43%) dose groups at week 5 and for the high (30%) dose group (30%) at week 12. Urea levels were elevated for the low (32%), mid (46%) and high (44%) dose groups for the females at week 12 but no statistically significant increases were evident at week 5. The study report recognized these increases as not being "always dose related" but still considered the effect to be a result of resmethrin exposure.

The blood levels of Na^+ (about up to 5%) and Ca^{++} (also about up to 5%) were decreased and the testing laboratory asserted that the effects on these elements may have been related to the presence of resmethrin.

Other deviations from the control were found for alkaline phosphatase (increased 27 to 43% for males at 12 weeks for all dosed groups). Glutamic pyruvate transaminase was also decreased slightly for the male high-dose group at 12 weeks (-31% . Cholesterol levels were decreased (19 to 34%) for males at both weeks 5 and 12 but no dose response was evident. The differences in

these parameters relative to the control, although statistically significant, were not considered by the testing laboratory to be related to the exposure to resmethrin.

Overall, this study does not clearly demonstrate a NOEL for depression of blood levels of glucose. The observation of an apparent effect on blood glucose levels is not supported by a similar finding in the chronic feeding study with resmethrin. Urea levels in females were also elevated at the lowest test dose for at week 12 and at other dose levels for males at week 5 and 12.

9. Urinalysis - Urine was collected from fasted animals at weeks 5 and 12. The CHECKED (X) parameters were examined.

	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity		Bilirubin
X	pH		Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen
X	Total reducing substances	X	Bile pigments
X	Hemoglobulin pigments		

Results - No treatment-related effects of resmethrin exposure to the rats were recognized by the testing laboratory There were some deviations from the control values with regard to urine volume, pH, and lower protein concentrations but these were not considered to be related to resmethrin exposure.

Note: Glucose levels were estimated by a qualitative test and no values were reported in the data tables, meaning no glucose was detected.

10. Organ Weights - At termination, the adrenals, brain, heart, kidneys, liver, lung, ovaries, pituitary, spleen, testes, thymus (when present), thyroids, and uterus were weighed. Of these organs the following were apparently affected by resmethrin exposure.

a) Liver - The high dose males (15.4% absolute, 21.5% relative) and females (24.8% absolute and 30.7% relative) were elevated.

b) Kidney - All exposed groups were elevated for the females (5.3, 6.8, and 8.4% for absolute and 9.2, 9.9, and 13.6% for relative weight for the low-,

mid-, and high-dose groups). Among the males the mid- (10.9%) and high- (5.8%) for absolute weight and 9.0 and 11.5% for relative weight dose groups were elevated. The testing laboratory dismissed this finding as not being related to exposure to resmethrin because of the small increase and lack of a clear increase with increase in dose levels.

c) Thyroid - The high-dose group males had higher thyroid weights (12% absolute and 18.1% relative) but the females (although they were 14.3% higher for absolute weight than controls) did not reach statistical significance.

d) Testes - The high-dose group testes weight was elevated (3.1% absolute weight).

e) Uterus - The high-dose group uterus weight was elevated (34% absolute weight).

The increases in weight noted for the kidneys, testes, or uterus were not supported by histological changes (see below). Thus, it is not conclusive that the weight changes in these tissues were due to exposure to resmethrin.

11. Necropsy - The protocol called for a detailed macroscopic examination of each individual rat.

The study report maintains that there were no treatment-related changes. Inspection of the summary table (Table 18) would support that conclusion. It was noticed by this reviewer, however, that 2 of the females (of 16) had "liver, enlarged" in the high-dose group. None of the other rats had this condition.

It was also noted that the rats allowed to recover had "enlargement of the cervical lymph nodes" in 6/9 males and 4/9 females. There was only a single incidence of this condition among all the rats examined at termination of exposure. There was no control group of the same age to determine if there was an effect.

12. Histopathology - A comprehensive list of 44 tissues were preserved for microscopic examination. Of these, some 35 tissues were scheduled for examination for 10 rats of each sex for the control and high-dose groups. The tissues from the rats in the low- and mid-dose groups were examined if the tissue showed some indication of an effect in the high-dose group. The lungs from all rats were examined.

The following is an organ-by-organ discussion of the findings.

a) Larynx - The rats in the high-dose group were reported to have "minimal epitheliai acanthosis ± hyperkeratosis in the ventral and/or over the arytenoid cartilage in the majority of rats in the high-dose group." The low- and mid-dose group rats after termination of exposure and the high-dose group following recovery were not reported as having this lesion.

b) Liver - The liver of both sexes in the high-dose group had elevated weight and it was noted that at least some of the females in this group had "liver enlargement."

Pathological changes in the liver were not obvious and special sectioning and analysis were required which included examination with a "comparison microscope." No evidence of "centrilobular hepatocyte enlargement but possible generalized hepatocyte enlargement" was suspected in some treated rats. This was evident by the count of hepatocytes in a given rectangular field which was decreased for both males (16.7 versus 15.2) and females (19.7 versus 18.3). When combined, the difference between the high-dose group (16.76) and the control (18.22) was statistically significant ($p < .01$). The male recovery group was only 15.7 but there was no control group of the same age to determine if there was an effect.

c) Thyroids - There was noted an increase in rats showing "minimal increased follicular height" in the high-dose group as shown in the following table taken from the study report.

Thyroids Minimal Increase in Follicular Height			
1 M	3/10	1 F	0/10
2 M	1/10	2 F	0/10
3 M	1/10	3 F	1/10
4 M	6/10	4 F	6/10
4 M Recovery	1/9	4 F Recovery	0/9

Conclusions

This study is classified as CORE GUIDELINES.

The following one-liner applies.

NOEL < 0.1 mg/L - At this level, signs of "sneezing" and "agitated grooming" were evident during exposure 27 and apparently afterwards. Glucose levels decreased in males. Females showed decreased weight gain (-13%) during weeks 1-4 and serum levels of urea were elevated 32%.

At 0.3 mg/L - These symptoms intensified and started at exposure 10 and other clinical signs were evident which included "rubbing the paws on the face," "adoption of a prone posture," and "red staining of the snout." Glucose levels decreased in males and females. Females showed a decreased weight gain (-13%) during weeks 1-4. Serum levels of urea were elevated for males at week 5 and for females at week 12.

At 1.0 mg/L - These same symptoms were evident and other signs of irritation to the atmosphere were evident including decreased locomotor activity and grooming activity, tremors (when handled), convulsions (one male and two females), and single incidences of extensor thrust abolished and of vocalization. Decreased weight gain in males and females. Decreased blood glucose levels and elevated albumin/globulin ratio. Possible decrease in blood levels of Na^{+} and Ca^{++}. Increased liver weight, generalized lymphocyte enlargement, and "minimal increase in follicular height" of the thyroid. Thyroid, testes and uterus showed increased weights. Serum levels of urea were elevated at weeks 5 and 12 for males and at week 12 for females.

The testing laboratory maintains that the effects on serum glucose (a decrease) were related to resmethrin exposure but a similar effect was not also evident when resmethrin was tested orally. The decrease in blood glucose level was not supported by any other indication of a toxic response to resmethrin exposure such as an endocrine effect. (Note: the increase in follicular height in the thyroid would, if anything, probably result in an increase in blood glucose levels, but there was no evidence that the thyroid lesions resulted in a systemic change in the rats and this increase was noted only in the high dose test group.]