D-9214 / Bioallethrin

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

JUL 15 1987

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cover Memo for Bioallethrin Registration Standard

FROM. Pamela M. Hurley, Toxicologist Pamela M. Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

TO: Richard King, PM Team #17
Insecticide-Rodenticide Branch
Registration Division (TS-767c)

THRU: for Amy Rispin, Chief Fred Betz
Science Integration Staff
Hazard Evaluation Division (TS-769c)

The Bioallethrin Registration Standard covers two active ingredients: d-trans-chrysanthemic acid of d-allethrolone and d-trans-chrysanthemic acid of l-allethrolone. Both active ingredients are registered in five products: Bioallethrin, s-Bioallethrin (Esbiol), Allethrin, Pynamin Forte and Esbiothrin. In addition, there are up to six other stereoisomers present in each of these products which are considered manufacturing impurities from the production of the active ingredients. See the accompanying chart for the percent of each of the stereoisomers in the manufacturing products. The major producers of the bioallethrins are the McLaughlin Gormley King Company, Prentice Drug, Fairfield American, Sumitomo Chemical Company and Roussel Uclaf.

The bioallethrins are broad spectrum synthetic insecticides and acaricides commonly used to control a variety of urban insect pests including cockroaches, ants, fleas, flies, mosquitoes, lice and ticks. They are formulated as dusts, impregnated materials (such as mosquito coils), emulsifiable concentrates, soluble concentrate/liquids, ready-to-use liquids and pressurized liquids.

Usage data from BUD's Economic Analysis Branch indicate that domestic dwellings (indoor) and domestic dwellings (outdoor) are high volume sites and commercial establishments are low volume sites. Bioallethrin comprises the largest segment of the market with nearly one-half of the total allethrins usage (primarily in indoor room foggers and plant, carpet and general use aerosols). Allethrin accounts for about a quarter

of the usage (primarily mosquito coils). Pynamin Forte accounts another quarter of the usage (outdoor air foggers). The others are considered to be minor uses.

In general, Bioallethrin and s-Bioallethrin are used on nonfood agricultural crops, ornamental plants and forest trees, in recreational areas and domestic indoor and outdoor areas (including sprays, dusts and foggers), on stored agricultural crops such as dried fruit (not sprayed directly on fruits), on stored processed food, in farm milk houses and horse barns, in food handling establishments (including food processing plants, eating establishments and supermarkets) and in commercial areas. Currently, no tolerances or exemptions from the requirement of a tolerance have been established to cover residues occurring in or on foods as a result of these uses.

Allethrin has tolerances and exemptions from the requirement of a tolerance and is used on terrestrial and greenhouse food and nonfood crops, in farm animal quarters d food handling establishments, and also has domestic indoor and outdoor uses as well as aquatic and forestry uses. At the present time, Pynamin Forte is used on terrestrial and greenhouse nonfood crops, in food processing plants, and in domestic indoor and outdoor situations. It is expected that tolerances will be required to cover residues in or on foods resulting from preharvest use on terrestrial and greenhouse food crops (exemptions will be revoked), and use on stored food, in farm animal quarters and milking houses, on horses and in food handling establishments. Currently, residues resulting from these uses are not covered by tolerances or are exempt from the requirement of a tolerance (40 CFR 180.1002).

HED CONCERNS

There are major data gaps in the areas of environmental fate and potential exposure to humans and nontarget organisms, residue chemistry and toxicology. The areas of concern are the potential for cumulative residues occurring in or on food items as a result of preharvest and postharvest treatments, the use of bioallethrins in food handling establishments and the toxicity of bioallethrins to nontarget aquatic organisms resulting from outdoor applications.

ECOLOGICAL EFFECTS

Terrestrial

The bioallethrins are considered to be nontoxic to moderately toxic to honey bees, but residual toxicity testing will not be required because the outdoor use rates are so low that even direct application to bees is not likely to result in significant mortality. No other data are required for nontarget insect studies. The bioallethrins are practically nontoxic to waterfowl in acute studies and practically nontoxic to slightly toxic to birds in subacute studies. Their uses are not expected to pose a risk to nontarget wildlife. No specific labeling is required for honey bees or avian species. There is no endangered species problem.

Aquatic

The available data indicate that the bioallethrins are very highly toxic to both coldwater and warmwater fish species. In addition, the available data indicate that the bioallethrins are very highly toxic to freshwater aquatic invertebrates. Because the environmental fate of bioallethrins has not been adequately characterized, there are insufficient data to assess the risk to aquatic organisms. Therefore, additional data may be required if the chemicals demonstrate persistence in the environment. These studies are reserved pending receipt of the following data: application frequency and timing, environmental stability and movement of the compound. Due to the high toxicity, precautionary labeling is required for fish for both manufacturing-use products and end-use products. Labeling requirements for endangered species are reserved pending the environmental fate data.

Ecological Effects Data Requirement Summary

The following data are required (but held in reserve pending receipt of the environmental fate data and depending upon use pattern) for all outdoor uses.

Avian reproduction
Field testing - mammals and birds (reserved pending reproduction data)
Freshwater fish LC_{50} (typical end-use product)
Freshwater aquatic invertebrate LC_{50} (typical end-use product)
Acute estuarine and marine LC_{50} (fish, shrimp, oyster)
Fish early life stage and invertebrate life cycle (freshwater, estuarine)
Fish life cycle
Field testing (aquatic organisms)

ENVIRONMENTAL FATE

The available data are insufficient to fully assess the environmental fate and transport of, and the potential exposure of humans and nontarget organisms to the bioallethrins.

Re-entry

Data are not available to assess the exposure of workers reentering fields after application of bioallethrins. Bioallethrin and Allethrin are used on crops where human exposure could occur, but available toxicology data do not indicate that they meet any of the toxicity criteria. Therefore, no data are required at this time. However, if the results of the toxicology testing requirements indicate that either one and/or the other does meet any of the toxicity criteria, reentry data will be required. Until appropriate data are developed, a 24-hour reentry interval is proposed.

Groundwater

No adequate data are currently available to assess the potential for the bioallethrins to contaminate groundwater. However, there are no indications that give rise to any concerns at this time.

Environmental Fate Data Requirements

The Environmental Fate data requirements will be approached using a tier testing system. The tier approach is based upon the judgement that the bioallethrins are photolabile and that all the isomers are expected to behave similarly. Whether or not the tests in tier II will be required will depend upon the results from the tests in tier I. If the tests in tier I indicate that the bioallethrins do not photodegrade rapidly and that they tend to be persistent, then the tests in tier II will be required. The results from the tier I tests will also determine what additional tests will be required for ecological effects.

The following list summarizes the environmental fate data requirements for each of the bioallethrins.

DEGRADATION STUDIES-LAB
hydrolysis — TIER I
photodegradation - water, soil, air
METABOLISM STUDIES - LAB
aerobic metabolism (soil, aquatic)
anaerobic metabolism in soil
MOBILITY STUDIES
leaching/aged leaching
volatility (lab)

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anaerobic metabolism in water Reserved — TIER II
field dissipation (soil) Reserved
field dissipation (aquatic sediment) Reserved
field dissipation (soil, long-term) Reserved
accumulation studies on rotational crops (confined) Reserved
accumulation studies on rotational crops (field) Reserved
accumulation studies on irrigated crops Reserved
accumulation studies in fish Reserved
accumulation studies in aquatic nontarget organisms Reserved

RESIDUE CHEMISTRY

Product Chemistry

The Agency has determined that product chemistry data for all technical and manufacturing-use products must be resubmitted for each pesticide because new requirements have been introduced and previously submitted data must be updated. The following generic data requirements are being required through the Registration Standard. Specific details on the requirements are provided in the tables.

Product identity and composition
Analysis and certification of product ingredients
Physical and chemical characteristics

Residue Chemistry: Tolerance Reassessment

The available data are insufficient to evaluate the adequacy of the established tolerances (covering postharvest use) for residues of bioallethrins in or on the food/feed items listed in 40 CFR 180.113. The available data are also insufficient regarding the magnitude of residues in or on a variety of food and feed crops following registered preharvest use or treatment of food handling establishments. In addition, plant and animal metabolism data, storage stability data, and residue data depicting residues in meat, milk, poultry, and eggs following direct treatment and/or ingestion of residues are required.

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Residue Chemistry Data Requirement Summary

For each data requirement listed below regarding the "Magnitude of the Residue", the specific end-use formulation to be tested will be the one in which its particular use (a use relating specifically to the data requirement) will most likely result in the maximum amount of residue in foods. It is assumed that the results of the studies will be similar for any of the other bioallethrins with similar use patterns. For the metabolism studies, Allethrin will be tested with all eight of its isomers.

Nature of the residue (metabolism) in plants and livestock
Residue analytical methods - (may be required if additional metabolites of toxicological concern identified)
Storage stability data
Magnitude of the residue
  Crop field trials
  Postharvest treatment of fruits and vegetables
  Stored commodities
  Processing studies
  Meat/milk/poultry/eggs
  Food handling

TOXICOLOGY

The required toxicity studies will include any acute toxicity studies for which there is a data gap for each of the 5 products, Bioallethrin, Allethrin, Pynamin Forte, s-Bioallethrin and Esbiothrin. The required chronic studies for Bioallethrin, s-Bioallethrin and Esbiothrin will be satisfied by chronic studies conducted on Esbiothrin as a representative for the three products. The required chronic studies for Allethrin and for Pynamin Forte are to be conducted separately. The rationale for this decision is given below.

In evaluating the toxicology data base, the Toxicology Branch (TB) took into consideration a previous request from a Registrant concerning a data call-in notice for the bioallethrins. The Registrant requested that one of their products, Esbiothrin be tested in chronic studies as a representative for Bioallethrin and s-Bioallethrin. Esbiothrin is a combination of Bioallethrin and s-Bioallethrin (60% s-Bioallethrin, 40% Bioallethrin). After considering the available chemistry and toxicology data, TB accepted the request. Since Esbiothrin is a registered product, the appropriate acute toxicity data for this product is being requested in the Standard as well.

Acute toxicity

There are no sufficient acute toxicity data available for technical Allethrin and Pynamin Forte. The d-trans chrysanthemic acid of d-allethrolone isomer is more acutely

toxic via the oral route than the d-trans chrysanthemic acid of l-allethrolone. Therefore, since s-Bioallethrin and Esbiothrin have more of this isomer than Bioallethrin, the acute oral toxicities of the former two products are in category II and the acute oral toxicity of Bioallethrin is in category III. The acute dermal toxicity Esbiothrin is in category III. Esbiothrin is minimally irritating to rabbit eyes and slightly irritating to rabbit skin. The appropriate additional acute studies in all categories except acute delayed neurotoxicity studies are being required for all the allethrins in order to fully assess the acute toxicity characteristics of these products.

Subchronic Toxicity

The requirement for a rodent subchronic oral study for Pynamin Forte is satisfied with the existing adequate chronic 2-year rat feeding study. The requirement for a nonrodent subchronic oral study for Bioallethrin is satisfied with the existing 6-month chronic dog study. Subchronic rodent and nonrodent oral feeding studies are required for all the bioallethrins except for the specific studies mentioned above. In addition, 21-day dermal studies are required for all the bioallethrins and 90-day inhalation studies may be required depending upon the exposure assessment.

Chronic Toxicity, Oncogenicity and Reproductive Effects

A 2-year rat feeding study has been conducted on Pynamin Forte. The NOEL's were 6.6 mg/kg/day for females and 5.9 mg/kg/day for males based upon decreased body weight gains and the presence of histiocyte "phagocyting" crystals in the livers of females and increased liver weights in males. The LOEL's are 24.5 mg/kg/day for males and 28.6 mg/kg/day for females. Under the conditions of the study, Pynamin Forte did not prove to be an oncogen.

A six-month dog feeding study was conducted on Bioallethrin. and is considered to be acceptable as fulfilling the requirements for a chronic nonrodent feeding study on Bioallethrin. The NOEL was 200 ppm and the LOEL was 1000 ppm based upon centrilobular hydropic degeneration of the liver in both sexes. There was supporting clinical chemistry evidence.

No other chronic and/or oncogenicity feeding studies have been conducted on any of the other bioallethrins. In addition, no reproduction studies have been conducted. Therefore, chronic/oncogenicity rodent studies, chronic nonrodent feeding studies and reproduction studies are being required for all the bioallethrins except for the specific studies described above. In light of this, the Toxicology Branch

(TB) has approved testing Esbiothrin as a representative for Bioallethrin and for s-Bioallethrin in chronic rodent and nonrodent feeding studies, in oncogenicity studies in rodents and in a reproduction study. Data from these studies conducted on Esbiothrin will satisfy the chronic testing requirements for Bioallethrin and for s-Bioallethrin. Chronic/oncogenicity studies and reproduction studies will be separately required for Allethrin and for Pynamin Forte.

A teratology study has been conducted in the rat on Bioallethrin. The NOEL for maternal toxicity was 125 mg/kg/day based upon maternal deaths. The LOEL was 195 mg/kg/day. The NOEL for fetotoxicity could not be established because there was an increase the the number of fetuses with rudimentary 14th ribs at all levels. NOEL for teratogenicity was 195 mg/kg/day (Highest dose level tested). No other adequate teratology studies have been conducted with any of the other allethrins. Studies are required for all the bioallethrins in two species with the exception of the study described above.

Mutagenicity

Esbiothrin is not mutagenic in a reverse mutation test in Salmonella typhimurium at dose levels up to 5000 micrograms/plate. It also tested negatively in a mammalian cell forward mutation study at dose levels up to 80 micrograms/ml without metabolic activation and dose levels up to 120 micrograms/ml with metabolic activation. Bioallethrin tested negatively in a DNA damage and repair study in E. coli at dose levels up to 500 micrograms/plate and in a reverse mutation study in Salmonella typhimurium at dose levels up to 5000 micrograms/plate. No other acceptable mutagenicity studies were conducted on any of the other bioallethrins. With the exception of the specific studies described above, mutagenicity studies testing for gene mutation, chromosomal aberrations and other mechanisms of mutagenicity are required for all the bioallethrins.

Special Studies - Metabolism

Metabolism studies have not been conducted on any of the bioallethrins. These studies are required in the Standard.

Toxicology Data Requirement Summary

Acute toxicity

Acute oral LD_{50} toxicity (Allethrin, Pynamin Forte)
Acute dermal LD_{50} toxicity (Allethrin, Pynamin Forte, s-Bioallethrin, Bioallethrin)
Acute inhalation LC_{50} toxicity (all bioallethrins)
Eye irritation (all bioallethrins except Esbiothrin)
Dermal irritation (all bioallethrins except Esbiothrin)
Dermal sensitization (all bioallethrins)

In addition to the above, all the acutes except acute delayed neurotoxicity are required for the manufacturing-use products of each bioallethrin.

Subchronic Toxicity

90-day feeding
  Rodent (all bioallethrins except Pynamin Forte)
  Nonrodent (all bioallethrins except Bioallethrin)
21-day dermal (all bioallethrins)
90-day inhalation (reserved for all bioallethrins)

Chronic Toxicity

Rodent feeding (all bioallethrins except Pynamin Forte)
Nonrodent feeding (all bioallethrins except Bioallethrin)
Rat oncogenicity (all bioallethrins except Pynamin Forte)
Mouse oncogenicity (all bioallethrins)
Rat teratogenicity (all bioallethrins except Bioallethrin)
Rabbit teratogenicity (all bioallethrins)
Reproduction (all bioallethrins)

Mutagenicity

Gene mutation (Allethrin, Pynamin Forte, s-Bioallethrin)
Chromosomal aberration (all bioallethrins)
Other mechanisms of mutagenicity (all bioallethrins except Bioallethrin)

Special Testing

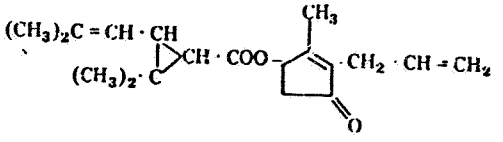
Metabolism (all bioallethrins)

CHART

Composition of Products in the Bioallethrin Series Addressed in this Registration Standard

Stereoisomers / Active Ingredients	Products (% composition)				
	Allethrin	Bio-allethrin	Es-biothrin	d-Bio-allethrin	Pynamiforte
d-transChrysanthemic acid of d-allethrolone (d-trans of d)	18	≥ 46.5	72	>90	36.5
d-transChrysanthemic acid of L-allethrolone (d-trans of l)	18	≥ 46.5	21	± 5	36.5
Manufacturing Impurities					
l-trans of d	(38)	trace	trace	--	--
l-trans of l		trace	trace	--	--
d-cis of d	(9)	± 0.5	trace	--	(18.4)
l-cis of l		± 5	trace	--	
d-cis of d	(9)	trace	trace	--	--
l-cis of l		trace	trace	--	--

Chemical Structure:



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APR 30 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Bioallethrin, Toxicology Chapter of the Registration Standard

TO: Richard King, PM Team #17 Tox. Chem. No. 25A
Insecticide-Rodenticide Branch
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THROUGH: Robert P. Zendzian, Ph.D. 4/15/87
Registration Standard Coordinator
Toxicology Branch
Hazard Evaluation Division (TS-769c)

William Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769c)

Attached is the Toxicology Chapter of the Registration Standard for Bioallethrin. This Standard includes Bioallethrin, Esbiol and Esbiothrin.

cc:
A. Rispin, SIS
R. Zendzian
R. Coberly

Toxicology Chapter
Bioallethrin
(Esbiol and Esbiothrin)
Registration Standard

Pamela M. Hurley, Ph.D.
Toxicologist, Section II
Toxicology Branch
Hazard Evaluation Division

Toxicology Chapter

Table of Contents

A. Toxicology Summary

The Toxicology Chapter of the Registration Standard for Bioallethrin contains a discussion of the available toxicology data for three technical products, all of which are composed of nearly identical mixtures of synthetic pyrethroid isomers, except that each technical product contains the two major isomers in different proportions. The three technical products are Bioallethrin, Esbiothrin and Esbiol (S-Bioallethrin). The percentages of the two major isomers, d-trans chrysanthemic acid of d-allethrolone and d-trans chrysanthemic acid of l-allethrolone in the three technical products are as follows: Bioallethrin (46.5% : 46.5%), Esbiothrin (72% : 21%) and Esbiol (90% : 5%), respectively.

Since the three technical products are nearly identical except in the ratios of the two major isomers, the Toxicology Branch (TB) made a previous decision in a response to a Data Call-In request from a Registrant to accept test results on Esbiothrin as satisfying registration requirements for all three technical products for the following toxicity studies: chronic, reproductive and oncogenicity (Hurley 1986). The same decision applies to this Registration Standard. All three of the technical products will, however, be required to be tested in all of the other studies required for registration. This also applies to the subchronic oral studies since results from these will be used to verify that the chronic studies performed on Esbiothrin will safely predict the potential toxic effects of the other two products.

Bioallethrin

Bioallethrin is mainly used as an insecticide in sprays, aerosols and in dusting powders to be used against household insects. It is not highly toxic via the oral route in rats (LD_{50}'s: 709 mg/kg (males), 1041.9 mg/kg (females)) and is probably less acutely toxic in rats via the dermal route (LD_{50}>5000 mg/kg, females; the acute dermal study lacked sufficient details for a complete evaluation). No data are available on either acute toxicity via inhalation, eye and dermal irritation or on dermal sensitization.

In a subchronic feeding study in rats, the liver is the target organ. Increases in serum liver enzyme levels were observed in females following treatment and increases in liver weights were also noted in both sexes. In addition, decreased body weight gains were observed (NOEL 1500 ppm, LOEL 5000 ppm). No other subchronic toxicity studies are available on Bioallethrin.

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Subject: Testing Esbiothrin as Representative for Other

The liver is also the target organ in a chronic (6-month) feeding study in dogs. Centrilobular hydropic degeneration of the liver was observed in both sexes. The clinical chemistry studies provided supporting evidence of liver toxicity (NOEL 200 ppm, LOEL 1000 ppm). The study also indicates that the dog is likely to be more sensitive to the toxic effects of Bioallethrin than the rat.

Bioallethrin is not teratogenic in rats up to a dose level of 195 mg/kg/day. The NOEL for fetotoxicity cannot be determined from the study because of the increase in the number of fetuses with rudimentary 14th ribs at all dose levels tested (50 mg/kg/day, LDT). The NOEL for maternal toxicity (based upon death of the dams) is 125 mg/kg/day.

No oncogenicity, reproductive or other chronic toxicity studies are available on Bioallethrin.

Bioallethrin tested negatively in a growth inhibition (DNA damage and repair) assay in E. coli up to a dose level of 500 micrograms/plate and in a bacterial gene mutation assay up to a dose level of 5 mg/plate. It also tested negatively in a mouse micronucleus (chromosomal damage) assay, but incomplete data were submitted for the study.

No metabolism studies are available on Bioallethrin.

No food additive tolerances exist for the use of Bioallethrin in food processing or warehousing situations. No tolerances exist for either milk or meat animals and no recommendations exist for use on crops.

Esbiol

Esbiol, as with Bioallethrin, is used as a knockdown or flushing agent for household crawling insects and is generally a component of either an aerosol or a spray. It is more acutely toxic via the oral route in rats than Bioallethrin (LD_{50}'s: 575 mg/kg (males), 413 mg/kg (females)). This is partially explained by the fact that it contains more of the d-allethrolone isomer, which is not only more acutely toxic than the l-isomer, but it is also the most effective isomer as an insecticide. It appears to be a minimal eye irritant, but the lack of a scoring method in the study does not allow for an adequate evaluation. Dermal irritation studies in rats and rabbits indicate that Esbiol is not an irritant, however, a complete evaluation of the study cannot be conducted due to inadequate reporting. The study also indicates that Esbiol is dermally toxic to rats, however, an acute dermal LD_{50} study is not available. No data are available on acute inhalation toxicity or on dermal sensitization.

Subchronic feeding studies in rats (90 days and 6 months) do not give any indications of any significant toxic effects up to the maximum dose levels tested (0.3% in diet (males) and 0.15% in diet (females)). However, insufficient histopathology examinations were conducted in these studies. No other subchronic studies are available.

Teratology studies on Esbiol indicates that it is not a teratogen in rats and mice up to a dose level of 0.1 ml/kg. However, the dosing schedules did not cover all of the organogenesis periods and insufficient details were submitted with the studies on both the procedures followed and the results obtained.

No studies are available on the chronic toxicity, oncogenicity or reproductive toxicity of Esbiol.

No mutagenicity studies are available on Esbiol.

No metabolism studies are available on Esbiol.

No food additive tolerances exist for Esbiol. No tolerances exist for use on milk and meat animals. No recommendations exist for use on food crops.

Esbiothrin

Esbiothrin is a mixture of Bioallethrin and Esbiol. The acute oral toxicity of Esbiothrin in rats is similar to that of Esbiol (it contains more of the d-allethrolone isomer than Bioallethrin and less of the isomer than Esbiol; LD_{50}'s: 432.3 mg/kg (males), 378 mg/kg (females)). The acute dermal toxicity of Esbiothrin in rabbits (LD_{50}>2000 mg/kg) is considerably less than its acute oral toxicity in rats and is probably less acutely toxic to rats via the inhalation route (data needs to be recalculated). It is minimally irritating to the eye and slightly irritating to the skin of rabbits. No data are available on dermal sensitization.

No subchronic studies are available on Esbiothrin.

No studies are available on the chronic toxicity, oncogenicity, teratogenicity or reproductive toxicity of Esbiothrin.

Esbiothrin is negative in a bacterial gene mutation test up to a dose level of 5 mg/plate and in a mammalian cell forward mutation test up to dose levels of 80 micrograms/ml without activation and 120 micrograms/ml with activation. It is also negative in a mouse micronucleus test (chromosomal aberration), but the data presented were inadequate for a definitive conclusion.

No metabolism studies are available on Esbiothrin.

No food additive tolerances exist for Esbiothrin. No tolerances exist for its use on milk and meat animals. No recommendations exist for use on food crops.

B. Toxicology Profile

1. Bioallethrin

81 Series Acute Toxicity and Irritation Studies

81-1 Acute Oral

Sufficient data are available to show that Technical Bioallethrin has a low acute oral toxicity to mammals (MRID 0015144). The acute oral LD_{50} in polyethyleneglycol 200 for rats is 709 (397.9-1756.0) mg/kg (males) and 1041.9 (805.8-1348.7) mg/kg (females). Toxicity Category III.

81-2 Acute Dermal

No adequate acute dermal study is available for Technical Bioallethrin. A supplementary study conducted on female rats indicates that the LD_{50} is greater than 5000 (3444-7250) mg/kg (MRID 0122491). The toxicity category is III. A new study is required.

81-3 Acute Inhalation

No acute inhalation study is available on Technical Bioallethrin. A study is required.

81-4 Primary Eye Irritation

No primary eye irritation study is available on Technical Bioallethrin. A study is required.

81-5 Primary Dermal Irritation

No primary dermal irritation study is available on Technical Bioallethrin. A study is required.

81-6 Dermal Sensitization

No dermal sensitization study is available on Technical Bioallethrin. A study is required.

81-7 Acute Delayed Neurotoxicity

No acute delayed neurotoxicity study is available on Technical Bioallethrin. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Bioallethrin is not an organophosphate, therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

No adequate subchronic oral study in rodents is available on Technical Bioallethrin. A supplementary subchronic oral feeding study in rats has been conducted in which the animals were fed dose levels of 0, 500, 1500, 5000 and 10000 ppm in the diet for 90 days (MRID 00122492). Sixteen rats/sex/dose level were tested; 5 rats/sex/dose level were sacrificed at 45 days. Decreases in body weight gain and increases in serum liver enzymes were noted in females and increases in liver weights were observed in both sexes. The NOEL is 1500 ppm and LOEL is 5000 ppm. There was a high incidence of respiratory infections in all groups, including controls.

Either a new study is required or this study may be upgraded if summary tables of the histopathology results are submitted. A subchronic oral toxicity study on Technical Bioallethrin in a rodent species will not be required if an acceptable chronic study on Technical Bioallethrin in a rodent species is submitted. However, it should be noted that the subchronic study is used for calculating the maximum tolerated dose for oncogenicity studies. If a chronic study on Esbiothrin is submitted in order to fulfill the requirement for a chronic study on Bioallethrin (see notation under chronic toxicity testing), then a subchronic study on Technical Bioallethrin is required.

No subchronic oral toxicity study in a nonrodent species is available on Technical Bioallethrin. A subchronic oral toxicity study in a nonrodent species is not required since a 6-month dog feeding study on Technical Bioallethrin is available.

82-2 Subchronic Dermal (21-day)

No 21-day dermal study is available on Technical Bioallethrin. A 21-day dermal study is required since repeated dermal exposure is expected when the pesticide is used in carpet insecticide powders and dusts.

82-3 Subchronic Dermal (90-day)

No 90-day dermal study is available on Technical Bioallethrin. A 90-day dermal study is not required for the registered use patterns.

82-4 Subchronic Inhalation

No subchronic inhalation study is available on Technical Bioallethrin. A subchronic inhalation study may be required if the use assessment indicates the need for such a study.

82-5 Subchronic Neurotoxicity

No subchronic neurotoxicity study is available on Technical Bioallethrin. The subchronic neurotoxicity study in the hen is not required since the acute toxicity study in the hen is not required. Occasionally, in this class of compounds, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals, especially if appropriate preservation and staining methods are employed.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

No chronic rodent study is available on Technical Bioallethrin. Either a study is required or as stated in the Toxicology Summary Section, a chronic rodent study on Esbiothrin will be accepted as having met the requirements for Technical Bioallethrin.

Sufficient data are available to satisfy the data requirements of a chronic toxicity study in a nonrodent species. A 6-month dog study conducted prior to the publication of the Subpart F Guidelines is accepted as satisfying the requirements for Technical Bioallethrin (MRID 00151447). Six male and 6 female dogs/group were tested for 6 months with the following dose levels in the diet: 0, 200, 1000 and 5000 ppm. Centrilobular hydropic degeneration of the liver was observed in both sexes. Supporting evidence was provided in the clinical chemistry studies (increases in the levels of serum AP, SGPT, GGTP and SGOT). The NOEL is 200 ppm and LOEL is 1000 ppm.

83-2 Oncogenicity

No data are available to evaluate the oncogenic potential of Technical Bioallethrin. Either life-time feeding studies in the rat and mouse are required or as stated in the Toxicology Summary Section, life-time feeding studies on Esbiothrin in the rat and mouse will be accepted as having met the requirements for Technical Bioallethrin.

83-3 Teratogenicity

Sufficient data are available on Technical Bioallethrin to satisfy the data requirements of a teratology study in one species.

Female pregnant rats were dosed with 0, 50, 125, 195 and 300 mg/kg/day during the period of organogenesis (MRID 00078624). The 300 mg/kg group was dropped due to high mortality of the dams. Technical Bioallethrin was not a teratogen under the conditions of the study. The feto-toxicity NOEL could not be established because of the increase in number of fetuses with rudimentary 14th ribs at all the dose levels tested. The maternal NOEL was 125 mg/kg/day (death of the dams).

A teratology study in a second species is required.

83-4 Reproduction

No data are available on the reproductive toxicity of Technical Bioallethrin. Either a study is required or as stated in the Toxicology Summary, a reproductive study conducted on Esbiothrin will be accepted as having met the requirements for Technical Bioallethrin.

84 Series Mutagenicity

84-2 Mutagenicity Tests

1. Gene Mutation

Sufficient data are available to evaluate the potential of Technical Bioallethrin to induce gene mutations.

Technical Bioallethrin was tested in the Ames Salmonella typhimurium assay (MRID 00133570). The chemical was tested both with and without metabolic activation (S-9 mix) in the following strains: TA 1537, TA 1538, TA 98, TA 1535 and TA 100. It tested negatively both with and without activation. In the assay with activation, weak positive responses (not statistically significant) were observed in TA 100 and TA 1535.

2. Structural Chromosomal Aberration

No adequate studies testing for chromosomal aberrations are available for Technical Bioallethrin. Two inadequate studies are available, one indicating positive results (MRID 00131594) and one indicating negative results (MRID 00133570). The positive study was conducted in Chinese Hamster lung cells. It is not known exactly what compound was tested. It is possible that Allethrin was tested instead of Bioallethrin. This study tested for chromosomal aberrations with metabolic activation (S-9 mix) only. The negative study tested Technical Bioallethrin in the mouse micronucleus test. The

compound was tested at dose levels which did not give any indications of toxicity, either clinical or cellular. Swiss CD-1 mice (5 males, 5 females/dose) were given 2 oral doses of Bioallethrin in sesame oil, 24 hours apart. The males received 100, 200 and 400 mg/kg and the females received 75, 150 and 300 mg/kg. It was claimed that these doses were close to the LD_{50} for mice.

A new study testing for the potential of Technical Bioallethrin to induce chromosomal aberrations is required. It is possible the the mouse micronucleus test can be upgraded if additional data are submitted.

3. DNA Damage and Repair

Sufficient data are available to assess the potential of Technical Bioallethrin to induce DNA damage.

A growth inhibition assay in E. coli was conducted with Technical Bioallethrin (MRID 00133570). The results with wildtype E. coli were compared with with 3 mutant strains which are deficient in certain repair mechanisms. The concentrations of Bioallethrin tested were: 1250, 2500 and 5000 micrograms/ml. The results were negative.

85 Series Special Studies

85-1 Metabolism

No data are available on the metabolism of Technical Bioallethrin. Studies are required.

85-2 Domestic Animal Safety

No data are available on domestic animal safety for Technical Bioallethrin. No studies are required.

85-3 Dermal Absorption

No data are available on the dermal absorption of Technical Bioallethrin. No studies are required since this compound does not have serious toxic effects identified in the oral and inhalation studies.

Information on Human Effects

No data are available on human studies with Technical Bioallethrin.

B. Toxicology Profile

(Continued)

2. Esbiol

81 Series Acute Toxicity and Irritation Studies

81-1 Acute Oral

Sufficient data are available to show that Technical Esbiol has a low acute oral toxicity to mammals (MRID 00151460). The acute oral LD_{50} in rats is 574.5 (399.6-742.1) mg/kg (males) and 412.9 (219.4-537.0) mg/kg (females). Toxicity Category II.

81-2 Acute Dermal

No acute dermal study is available on Technical Esbiol. A study is required.

81-3 Acute Inhalation

No acute inhalation study is available on Technical Esbiol. A study is required.

81-4 Primary Eye Irritation

No adequate eye irritation study is available on Technical Esbiol. A supplementary study in rabbits indicates that it is a minimal irritant, however, no scoring method was used in the study (MRID 00151466). A new study is required. The present study may be upgraded if it is scored with a method comparable to the Draize method commonly used for these studies.

81-5 Primary Dermal Irritation

No adequate dermal irritation study is available on Technical Esbiol. A supplementary study in rats and rabbits indicates that it is not dermally irritating to either of these species. The study is inadequately reported and the test design is unusual. Also, all the rats died after 36 hours due to dermal toxicity of the chemical (MRID 00151465).

81-6 Dermal Sensitization

No dermal sensitization study is available on Technical Esbiol. A study is required.

81-7 Acute Delayed Neurotoxicity

No acute delayed neurotoxicity study is available on Technical Esbiol. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Esbiol is not an organophosphate, therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

No adequate subchronic oral study in rodents is available on Technical Esbiol. Two supplementary subchronic oral feeding studies in rats have been conducted in which the animals were fed the following dose levels: males - 0.0.01, 0.03, 0.1 and 0.3% in the diet and females - 0, 0.005, 0.01, 0.03 and 0.15% in the diet for either 90 days or 6 months (MRID 00151470). Five animals/sex/dose were tested for 90 days and 10 animals/sex/dose were tested for 6 months. The NOEL's in both studies were 0.3% (HDT, males) and 0 15% (HDT, females). Histopathology was conducted on too few animals and in too few tissues. There was no baseline data for the hematology and clinical chemistry studies.

A new study is required. A subchronic oral toxicity study on Technical Esbiol in a rodent species will not be required if an acceptable chronic study on Technical Esbiol in a rodent species is submitted. However, it should be noted that the subchronic study is used for calculating the maximum tolerated dose for oncogenicity studies. If a chronic study on Esbiothrin is submitted in order to fulfill the requirement for a chronic study on Esbiol (see notation under chronic toxicity testing), then a subchronic study on Technical Esbiol in a nonrodent species is required.

No subchronic oral toxicity study in a nonrodent species is available on Technical Esbiol. A subchronic oral toxicity study on Esbiol in a nonrodent species is required. A subchronic oral toxicity study on Technical Esbiol in a nonrodent species will not be required if an acceptable chronic study on Technical Esbiol in a nonrodent species is submitted. If a chronic study on Esbiothrin in a nonrodent species is submitted in order to fulfill the requirement for a chronic study on Esbiol in a nonrodent species (see notation under chronic toxicity testing), then a subchronic study on Technical Esbiol in a nonrodent species is required.

84 Series Mutagenicity

84-2 Mutagenicity Tests

1. Gene Mutation

No gene mutation studies on Technical Esbiol are available. A study is required.

2. Structural Chromosomal Aberration

No chromosomal aberration studies are available on Technical Esbiol. A study is required.

3. Other Genotoxic Effects

No other genotoxic effect studies are available on Technical Esbiol. A study is required.

85 Series Special Studies

85-1 Metabolism

No data are available on the metabolism of Technical Esbiol. Studies are required.

85-2 Domestic Animal Safety

No data are available on domestic animal safety for Esbiol. No studies are required.

85-3 Dermal Absorption

No data are available on the dermal absorption of Technical Esbiol. No studies are required since this compound does not have serious toxic effects identified in the oral and inhalation studies.

Information on Human Effects

No data are available on human studies with Technical Esbiol.

82-2 Subchronic Dermal (21-day)

No 21-day dermal study is available on Technical Esbiol. A 21-day dermal study is required since repeated dermal exposure is expected under the conditions of use.

82-3 Subchronic Dermal (90-day)

No 90-day subchronic dermal study is available on Technical Esbiol. A 90-day dermal study is not required for the registered use patterns.

82-4 Subchronic Inhalation

No adequate subchronic inhalation study is available on Technical Esbiol. A supplementary inhalation study is available (MRID 00151467). Rats and mice were exposed to an aerosol containing Esbiol, 2 hrs/day, 6 days/week, for 1 month. The levels of exposure were 0.5%, 2.5% and 5.0% in deotomisol. The NOEL was 0.5% (clinical neurological signs). The mice were more sensitive than the rats. No particle size analyses were conducted. A new study may be required if the use assessment indicates the need for such a study.

82-5 Subchronic Neurotoxicity

No subchronic neurotoxicity study is available on Technical Esbiol. The subchronic neurotoxicity study in the hen is not required since the acute toxicity study in the hen is not required. Occasionally, in this class of compounds, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals, especially if appropriate preservation and staining methods are employed.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

No chronic rodent study is available on Technical Esbiol. Either a chronic rodent study on Esbiol is required or as stated in the Toxicology Summary Section, a chronic rodent study on Esbiothrin will be accepted as having met the requirements for Technical Esbiol.

No chronic toxicity study in a nonrodent species is available on Technical Esbiol. Either a chronic study in a nonrodent species on Technical Esbiol is required or as stated in the Toxicology Summary Section, a chronic study in a nonrodent species on Esbiothrin will be accepted as having met the requirements for Technical Esbiol.

83-2 Oncogenicity

No data are available to evaluate the oncogenic potential of Technical Esbiol. Either life-time feeding studies on Technical Esbiol in the rat and mouse are required or as stated in the Toxicology Summary Section, life-time feeding studies on Esbiothrin will be accepted as having met the requirements for Technical Esbiol.

83-3 Teratogenicity

No adequate studies are available to assess the potential teratogenicity of Esbiol. Two supplementary studies are available, one in rats and one in mice. In the rat study, the dams were administered 0.025, 0.05, 0.1 and 0.2 ml/kg (40x dilution in olive oil) during days 9-14 of pregnancy. The maternal NOEL was 0.025 ml/kg and the fetotoxicity NOEL was 0.1 ml/kg. There were no signs of teratogenicity. This study had an insufficient dosing schedule and the report contained too little detail in the conduct and design of the study and in the reporting of the results (MRID 00151471).

In the mouse study, the animals were dosed with 0.1 and 0.05 ml/kg (100x dilution in olive oil). In addition, the results from the preliminary study using 0.2 ml/kg were mixed in with the main results. The dams were dosed from days 7-12 of pregnancy. The maternal toxicity NOEL could not be established because of the difficulty in assessing the death rate and the high abortion rate (insufficient details were provided). The fetotoxicity NOEL was 0.1 ml/kg. There was no evidence of teratogenicity in this study. Again, there was an insufficient dosing schedule and insufficient details were provided in the methods and in the reporting of results (MRID 00151471).

Teratology studies on Esbiol in two species are required.

83-4 Reproduction

No data are available on the reproductive toxicity of Technical Esbiol. Either a reproductive study on Technical Esbiol is required or as stated in the Toxicology Summary Section, a reproductive study conducted on Esbiothrin will be accepted as having met the requirements for Technical Esbiol.

B. Toxicology Profile

(Continued)

3. Esbiothrin

81 Series Acute Toxicity and Irritation Studies

81-1 Acute Oral

Sufficient data are available to show that Technical Esbiothrin has a low acute oral toxicity to mammals (MRID PHES0001). The acute oral LD_{50} in polyethylene glycol is 432.3 (270.5-728.3) mg/kg (males) and 378.0 (219.3-555.6) mg/kg (females). Toxicity Category II.

81-2 Acute Dermal

Sufficient data are available to show that Technical Esbiothrin has a low acute dermal toxicity to mammals (MRID PHES0002). The LD_{50} in male and female rabbits is greater than 2000 mg/kg. Toxicity Category III.

81-3 Acute Inhalation

No adequate data are available to determine the acute inhalation toxicity of Esbiothrin. A supplementary study indicates that the combined LC_{50} in male and female rats is 2.63 g/m^3 (S.E. 0.207 g/m^3). Toxicity Category III (MRID PHES0003).

A study is required. This study may be upgraded if the data are recalculated and resubmitted.

81-4 Primary Eye Irritation

Sufficient data are available to assess the eye irritation potential of Technical Esbiothrin. An eye irritation study in rabbits shows that Esbiothrin is minimally irritating to the eye. The mean irritation score was 10. Toxicity Category IV (MRID PHES0004).

81-5 Primary Dermal Irritation

Sufficient data are available to assess the dermal irritation potential of Technical Esbiothrin. A dermal irritation study in rabbits shows that Esbiothrin is slightly irritating to the skin. The Primary Irritation Score was 1.05. Toxicity Category III (MRID PHES0005).

81-6 Dermal Sensitization

No dermal sensitization study is available on Technical Esbiothrin. A study is required.

81-7 Acute Delayed Neurotoxicity

No acute delayed neurotoxicity study is available on Technical Esbiothrin. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Esbiothrin is not an organophosphate, therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

No subchronic oral studies in rodents are available on Technical Esbiothrin. A study is required. A subchronic oral toxicity study in a rodent species will not be required if an acceptable chronic study on Technical Esbiothrin in a rodent species is submitted. However, it should be noted that the subchronic study is used for calculating the maximum tolerated dose for oncogenicity studies.

No subchronic oral toxicity studies in a nonrodent species are available on Technical Esbiothrin. A subchronic oral toxicity study in a nonrodent species will not be required if an acceptable chronic study on Technical Esbiothrin in a nonrodent species is submitted.

82-2 Subchronic Dermal (21-day)

No 21-day dermal study is available on Technical Esbiothrin. A 21-day dermal study is required since repeated dermal exposure is expected under the conditions of use.

82-3 Subchronic Dermal (90-day)

No 90-day subchronic dermal study is available on Technical Esbiothrin. A 90-day dermal study is not required for the registered use patterns.

82-4 Subchronic Inhalation

No subchronic inhalation studies are available on Esbiothrin. A study may be required if the use assessment indicates the need for such a study.

82-5 Subchronic Neurotoxicity

No subchronic neurotoxicity study is available on Technical Esbiothrin. The subchronic neurotoxicity study in the hen is not required since the acute toxicity study in the hen is not required. Occasionally, in this class of compounds, neurotoxic effects have been observed in mammals

in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals, especially if appropriate preservation and staining methods are employed.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

No chronic rodent toxicity study is available on Technical Esbiothrin. A study is required.

No chronic toxicity study in a nonrodent species is available on Technical Esbiothrin. A study is required.

83-2 Oncogenicity

No data are available to evaluate the oncogenic potential of Technical Esbiothrin. Life-time feeding studies in rats and mice are required.

83-3 Teratogenicity

No teratology studies are available on Technical Esbiothrin. Studies in 2 species are required.

83-4 Reproduction

No data are available on the reproductive toxicity of Technical Esbiothrin. A study is required.

84 Series Mutagenicity

84-2 Mutagenicity Tests

1. Gene Mutation

Sufficient data are available to assess the potential of Esbiothrin to induce gene mutation.

Esbiothrin was tested in a Salmonella typhimurium reverse mutation study (Ames Test, MRID PHES0006). The dose levels tested were 100, 500, 1000 and 5000 micrograms/plate, in the following strains: TA 1535, TA 100, TA 1537, TA 1538 and TA 98. The results were negative.

In a second study, Esbiothrin tested negatively in a mammalian cell forward mutation study (MRID PHES0008). It was tested in multiple dose levels in mouse lymphoma L5178Y cells up to cytotoxicity. both with and without metabolic activation.

2. Structural Chromosomal Aberration

No adequate studies testing for the potential to induce chromosomal aberrations are available on Esbiothrin. An unacceptable study indicates that Esbiothrin does not induce chromosomal aberrations in the mouse micronucleus test. Only one dose level was tested, there was no evidence of toxicity, either clinical or cellular and there was no evidence that the chemical reached the target tissue (MRID PHES0007). A new study is required.

3. Other Genotoxic Effects

No other genotoxic effect studies are available on Technical Esbiothrin. A study is required.

85 Series Special Studies

85-1 Metabolism

No data are available on the metabolism of Technical Esbiothrin. Studies are required.

85-2 Domestic Animal Safety

No data are available on domestic animal safety for Esbiothrin. No studies are required.

85-3 Dermal Absorption

No data are available on the dermal absorption of Technical Esbiothrin. No studies are required since this compound does not have serious toxic effects identified in the oral and inhalation studies.

Information on Human Effects

No data are available on human studies with Technical Esbiothrin.

C. Data Gaps

1. Bioallethrin

Bioallethrin is registered for the following types of uses: nonfood agricultural crops (terrestrial, aquatic and greenhouse), non-bearing citrus fruits, ornamental plants and forest trees, recreational areas, domestic indoor and outdoor (sprays, dusts and foggers), stored agricultural crops (i.e. dried fruits - not to be sprayed directly on fruits) and commercial. Bioallethrin is not registered for any tolerances. Therefore, the following Guideline toxicology studies can be required for this registration.

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral Dosing in Two Species (Rodent and Nonrodent)
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required)

83-1 Chronic Toxicity in Two Species (Rodent and Nonrodent)
83-2 Oncogenicity in Two Species
83-3 Teratogenicity in Two Species
83-4 Reproduction

84-2 Mutagenicity

85-1 Metabolism

Based on this assessment of the toxicology data base for Bioallethrin, the following Guideline Toxicology studies have been identified as data gaps and are required.

81-2 Acute Dermal Toxicity
81-3 Acute Inhalation
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral in Rodents
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required depending upon exposure assessment)

83-1 Chronic in Rodent*
83-2 Oncogenicity in Two Species*
83-3 Teratogenicity (Rabbit)
83-3 Reproduction*

*Studies conducted on Esbiothrin are acceptable.

84-2 Mutagenicity
This data requirement is only partially satisfied and additional testing is required for chromosomal aberration.

85-1 Metabolism

2. Esbiol

Esbiol is registered for the following types of uses: terrestrial nonfood crops (including ornamental plants and forest trees), recreational areas, domestic outdoor and indoor (sprays and foggers), stored agricultural crops such as dried fruit (not to be sprayed directly on fruit), domestic animals (not intended for food use) and commercial uses. Esbiol is not registered for any tolerances. Therefore, the following Guideline toxicology studies can be required for this registration.

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral Dosing in Two Species (Rodent and Nonrodent)
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required)

83-1 Chronic Toxicity in Two Species (Rodent and Nonrodent)
83-2 Oncogenicity in Two Species
83-3 Teratogenicity in Two Species
83-4 Reproduction

84-2 Mutagenicity

85-1 Metabolism

Based on this assessment of the toxicology data base for Esbiol, the following Guideline Toxicology studies have been identified as data gaps and are required.

81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral in Two Species (Rodent and Nonrodent)
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required depending upon exposure assessment)

83-1 Chronic in Rodent and Nonrodent*
83-2 Oncogenicity in Two Species*
83-2 Teratogenicity in Two Species
83-4 Reproduction*

84-2 Mutagenicity

85-1 Metabolism

* Studies conducted on Esbiothrin are acceptable.

3. Esbiothrin

Esbiothrin is a mixture of Bioallethrin and Esbiol. As such, it is not specifically registered separately from the other two Technical Formulations. It is probably registered for the same types of uses as Bioallethrin and Esbiol. Therefore, the following Guideline toxicology studies can be required for this registration.

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral Dosing in Two Species (Rodent and Nonrodent)
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required)

83-1 Chronic Toxicity in Two Species (Rodent and Nonrodent)
83-2 Oncogenicity in Two Species
83-3 Teratogenicity in Two Species
83-4 Reproduction

84-2 Mutagenicity

85-1 Metabolism

Based on this assessment of the toxicology data base for Esbiothrin, the following Guideline Toxicology studies have been identified as data gaps and are required.

81-3 Acute Inhalation Toxicity
81-6 Dermal Sensitization

82-1 Subchronic Oral in Two Species (Rodent and Nonrodent)
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation (may be required depending upon exposure assessment)

83-1 Chronic Toxicity in Two Species (Rodent and Nonrodent)
83-2 Oncogenicity in Two Species
83-3 Teratogenicity in Two Species
83-4 Reproduction

84-2 Mutagenicity
This data requirement is only partially satisfied and additional testing is required for chromosomal aberrations and other genotoxic effects.

85-1 Metabolism

D. ADI Reassessment

No tolerances have been approved for either Bioallethrin, Esbiol or Esbiothrin. Therefore, no ADI is required.

E. Toxicological Issues

The registered uses for these compounds indicate that it is possible that there may be significant repetitive human exposure to the compounds via inhalation. Subchronic inhalation studies on the compounds may be required depending upon the results from the exposure assessment.

The synthetic pyrethroids as a group have been known to induce neurotoxic damage at high dose levels. The Toxicology Branch has observed that in the past, if a chemical from this class does induce neurotoxic effects, the effects appear in subchronic and chronic studies. Therefore, special neurotoxicity studies are not necessary. The subchronic and chronic study protocols should be modified to include extra sections of the sciatic nerve and the spinal cord. In addition, *in situ* perfusion, special preservation and special staining techniques for these tissues should be used since hematoxylin and eosin do not always pick up the possible damage.

F. Toxicology Summary Tables

TABLE A
GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	B,D,F,G,H,I	Yes	0015144	No
81-2 - Acute Dermal	TGAI	B,D,F,G,H,I	No	---	Yes
81-3 - Acute Inhalation - Rat	TGAI	B,D,F,G,H,I	No	---	Yes
81-4 - Eye Irritation - Rabbit	TGAI	B,D,F,G,H,I	No	---	Yes
81-5 - Dermal Irritation - Rabbit	TGAI	B,D,F,G,H,I	No	---	Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI	B,D,F,G,H,I	No	---	Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	B,D,F,G,H,I	No	---	No 4/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	B,D,F,G,H,I	Partially	00122492	Yes 5/, 6/
Non-rodent	TGAI	B,D,F,G,H,I	No	---	No 7/

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal -	TGAI	B,D,F,G,H,I	No	---	Yes 4/
82-3 - 90-Day Dermal -	TGAI	B,D,F,G,H,I	No	---	No 9/
82-4 - 90-Day Inhalation -	TGAI	[Reserved] 10/	No	---	[Reserved] 10/
82-5 - 90-Day Neurotoxicity -	TGAI	B,D,F,G,H,I	No	---	No 11/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	B,D,F,G,H,I	No	---	Yes 12/, 13
Non-rodent	TGAI	B,D,F,G,H,I	Yes	00151447	No 14/
83-2 - Oncogenicity Study -					
Rat	TGAI	B,D,F,G,H,I	No	---	Yes 15/, 16
Mouse	TGAI	B,D,F,G,H,I	No	---	Yes 17/, 18
83-3 - Teratogenicity -					
Rat	TGAI	B,D,F,G,H,I	Yes	00078024	No
Rabbit	TGAI	B,D,F,G,H,I	No	---	Yes 19/
83-4 - Reproduction -	TGAI	B,D,F,G,H,I	No	---	Yes 20/

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	B,D,F,G,H,I	Yes	00133570	No
84-2 - Chromosomal Aberration	TGAI	B,D,F,G,H,I	No	---	Yes 21/,22/
84-2 - Other Mechanisms of Mutagenicity	TGAI	B,D,F,G,H,I	Yes	00133570	No
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B,D,F,G,H,I	No	---	Yes 23/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by case basis.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C= Aquatic, Food Crop; D = Aquatic, Non-Food; E= Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.

3/ Unless otherwise specified, data must be submitted no later than six months after publication of this Standard.

4/ This study is not required since the test article is not an organophosphate.

5/ The presently available Supplementary study may be upgraded if summary tables of the histopathology results are submitted.

6/ Subchronic feeding data on Technical Bioallethrin need not be submitted if chronic studies on Technical Bioallethrin in the rat are submitted. However, the Registrant should be aware that subchronic studies are useful and often necessary in determining the maximum tolerated dose (MTD) used for oncogenicity studies in rodents (mice and rats). If data are to be submitted, it must be submitted no later than 12 months after publication of this Standard. If a chronic study on Esbiothrin is submitted in order to fulfill the requirement for a chronic study on Bioallethrin (see footnote 12), then a subchronic feeding study on Technical Bioallethrin is required.

7/ A subchronic non-rodent feeding study is not required since an acceptable chronic dog feeding study was submitted.

8/ Data must be submitted no later than 7 months after the publication of this Standard.

9/ A 90-day dermal study is not required for this use pattern.

This requirement is reserved pending the receipt and review of the Exposure Assessment for this chemical.
This study is not required because the acute toxicity study in the hen is not required. Occasionally, in this class of chemicals, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals if appropriate preservation and staining techniques are employed.
An acceptable chronic rodent study on Esbiothrin will be accepted as having fulfilled the requirement for a chronic rodent study on Bioallethrin.
If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.
This study is a 6-month dog study conducted prior to publication of the Subpart F Guidelines. It is therefore accepted in this case as fulfilling the requirement for a chronic toxicity study in a nonrodent species.
An acceptable oncogenicity study on Esbiothrin in the rat will be accepted as having fulfilled the requirement for an oncogenicity study in the rat on Bioallethrin.
If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.
An acceptable oncogenicity study on Esbiothrin in the mouse will be accepted as having fulfilled the requirement for an oncogenicity study in the mouse on Bioallethrin.
If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.
The data must be submitted no later than 12 months after the publication of this Standard.
An acceptable reproduction study on Esbiothrin will be accepted as having fulfilled the requirement for a reproduction study on Bioallethrin. If it is decided that a new study will be conducted, the data must be submitted no later than 20 months after the publication of this Standard.
The presently available unacceptable study may be upgraded if additional data are submitted.
If a new study is to be conducted, the data must be submitted no later than 10 months after the publication of this Standard.
The data must be submitted no later than 14 months after the publication of this Standard.

F. To.. ology Summary Tables (Continued)

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING BIOALLETHRIN

Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
4.135 Toxicology				
CUTE TESTING:				
4-1 - Acute Oral - Rat	MP	No	-	Yes
4-2 - Acute Dermal	MP	No	-	Yes
4-3 - Acute Inhalation - Rat	MP	No	-	Yes
4-4 - Eye Irritation - Rabbit	MP	No	-	Yes
4-5 - Dermal Irritation - Rabbit	MP	No	-	Yes
4-6 - Dermal Sensitization - Guinea Pig	MP	No	-	Yes

1/ Composition: MP= Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.

TABLE A
GENERIC DATA REQUIREMENTS FOR ESBIOL

a Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
58.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	B,G,H,I	Yes	00151460	No
81-2 - Acute Dermal	TGAI	B,G,H,I	No	---	Yes
81-3 - Acute Inhalation - Rat	TGAI	B,G,H,I	No	---	Yes
81-4 - Eye Irritation - Rabbit	TGAI	B,G,H,I	No	---	Yes 4/
81-5 - Dermal Irritation - Rabbit	TGAI	B,G,H,I	No	---	Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI	B,G,H,I	No	---	Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	B,G,H,I	No	---	No 5/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	B,G,H,I	No	---	Yes 6/
Non-rodent	TGAI	B,G,H,I	No	---	Yes 7/

TABLE A
GENERIC DATA REQUIREMENTS FOR ESBIOL

ita Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
.58.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal -	TGAI	B,G,H,I	No	---	Yes 8/
82-3 - 90-Day Dermal -	TGAI	B,G,H,I	No	---	No 9/
82-4 - 90-Day Inhalation -	TGAI	[Reserved] 10/	No	---	[Reserved] 10
82-5 - 90-Day Neurotoxicity -	TGAI	B,G,H,I	No	---	No 11/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	B,G,H,I	No	---	Yes 12/, 1
Non-rodent	TGAI	B,G,H,I	No	---	Yes 14/, 1
83-2 - Oncogenicity Study -					
Rat	TGAI	B,G,H,I	No	---	Yes 16/, 1
Mouse	TGAI	B,G,H,I	No	---	Yes 18/, 1
83-3 - Teratogenicity -					
Rat	TGAI	B,G,H,I	No	---	Yes 20/
Rabbit	TGAI	B,G,H,I	No	---	Yes 21/
83-4 - Reproduction -	TGAI	B,G,H,I	No	---	Yes 22/

TABLE A
GENERIC DATA REQUIREMENTS FOR ESBIOL

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	B,G,H,I	No	---	Yes 23/
84-2 - Chromosomal Aberration	TGAI	B,G,H,I	No	---	Yes 24/
84-2 - Other Mechanisms of Mutagenicity	TGAI	B,G,H,I	No	---	Yes 25/
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B,G,H,I	No	---	Yes 26/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by case basis.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C= Aquatic, Food Crop; D = Aquatic, Non-Food; E= Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.
3/ Unless otherwise specified, data must be submitted no later than six months after publication of this Standard.
4/ The presently available Supplementary study may be upgraded if it is scored according to accepted scoring practices and resubmitted.
5/ This study is not required since the test article is not an organophosphate.
6/ Subchronic feeding data on Technical Esbiol need not be submitted if chronic studies on Technical Esbiol in the rat are submitted. However, the Registrant should be aware that subchronic studies are useful and often necessary in determining the maximum tolerated dose (MTD) used for oncogenicity studies in rodents (mice and rats). If data are to be submitted, it must be submitted no later than 12 months after publication of this Standard. If a chronic study on Esbiothrin is submitted in order to fulfill the requirement for a chronic study on Esbiol (see footnote 12), then a subchronic feeding study on Technical Esbiol is required.

7/ Subchronic feeding data on Technical Esbiol in a nonrodent species will not be required if an acceptable chronic study on Technical Esbiol in a nonrodent species is submitted. If data are to be submitted, it should be submitted no later than 12 months after the publication of this Standard. If a chronic nonrodent feeding study on Esbiothrin is submitted in order to fulfill the requirement for a chronic nonrodent feeding on Esbiol (see footnote 14), then a subchronic nonrodent feeding study on Esbiol is required.

8/ Data must be submitted no later than 7 months after the publication of this Standard.

9/ A 90-day dermal study is not required for this use pattern.

10/ This requirement is reserved pending the receipt and review of the Exposure Assessment for this chemical.

11/ This study is not required because the acute toxicity study in the hen is not required. Occasionally, in this class of chemicals, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals if appropriate preservation and staining techniques are employed.

12/ An acceptable chronic rodent study on Esbiothrin will be accepted as having fulfilled the requirement for a chronic rodent study on Esbiol.

13/ If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.

14/ An acceptable chronic nonrodent study on Esbiothrin will be accepted as having fulfilled the requirement for a chronic nonrodent study on Esbiol.

15/ If it is decided that a new study will be conducted, the data must be submitted no late than 42 months after the publication of this Standard.

16/ An acceptable oncogenicity study on Esbiothrin in the rat will be accepted as having fulfilled the requirement for an oncogenicity study in the rat on Esbiol.

17/ If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.

18/ An acceptable oncogenicity study on Esbiothrin in the mouse will be accepted as having fulfilled the requirement for an oncogenicity study in the mouse on Esbiol.

19/ If it is decided that a new study will be conducted, the data must be submitted no later than 42 months after the publication of this Standard.

20/ The data must be submitted no later than 12 months after the publication of this Standard.

21/ The data must be submitted no later than 12 months after the publication of this Standard.

22/ An acceptable reproduction study on Esbiothrin will be accepted as having fulfilled the requirement for a reproduction study on Esbiol. If it is decided that a new study will be conducted, the data must be submitted no later than 20 months after the publication of this Standard.

23/ The data must be submitted no later than 10 months after the publication of this Standard.

24/ The data must be submitted no later than 10 months after the publication of this Standard.

25/ The data must be submitted no later than 10 months after the publication of this Standard.

26/ The data must be submitted no later than 14 months after the publication of this Standard.

F. Toxicology Summary Tables (Continued)

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING ESBIOL

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING:				
81-1 - Acute Oral - Rat	MP	No	-	Yes
81-2 - Acute Dermal	MP	No	-	Yes
81-3 - Acute Inhalation - Rat	MP	No	-	Yes
81-4 - Eye Irritation - Rabbit	MP	No	-	Yes
81-5 - Dermal Irritation - Rabbit	MP	No	-	Yes
81-6 - Dermal Sensitization - Guinea Pig	MP	No	-	Yes

1/ Composition: MP= Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.

TABLE A
GENERIC DATA REQUIREMENTS FOR ESBIOTHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	B,D,F,G,H,I 4/	Yes	PHES0001	No
81-2 - Acute Dermal	TGAI	B,D,F,G,H,I	Yes	PHES0002	No
81-3 - Acute Inhalation - Rat	TGAI	B,D,F,G,H,I	No	---	Yes 5/
81-4 - Eye Irritation - Rabbit	TGAI	B,D,F,G,H,I	Yes	PHES0004	No
81-5 - Dermal Irritation - Rabbit	TGAI	B,D,F,G,H,I	Yes	PHES0005	No
81-6 - Dermal Sensitization - Guinea Pig	TGAI	B,D,F,G,H,I	No	---	Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	B,D,F,G,H,I	No	---	No 6/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	B,D,F,G,H,I	No	---	Yes 7/, 8/
Non-rodent	TGAI	B,D,F,G,H,I	No	---	Yes 9/, 10

TABLE A
GENERIC DATA REQUIREMENTS FOR ESBIOTHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisty This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal -	TGAI	B,D,F,G,H,I	No	---	Yes 11/
82-3 - 90-Day Dermal -	TGAI	B,D,F,G,H,I	No	---	No 12/
82-4 - 90-Day Inhalation -	TGAI	[Reserved] 13/	No	---	[Reserved] 13/
82-5 - 90-Day Neurotoxicity -	TGAI	B,D,F,G,H,I	No	---	No 14/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	B,D,F,G,H,I	No	---	Yes 15/
Non-rodent	TGAI	B,D,F,G,H,I	No	---	Yes 16/
83-2 - Oncogenicity Study -					
Rat	TGAI	B,D,F,G,H,I	No	---	Yes 17/
Mouse	TGAI	B,D,F,G,H,I	No	---	Yes 18/
83-3 - Teratogenicity -					
Rat	TGAI	B,D,F,G,H,I	No	---	Yes 19/
Rabbit	TGAI	B,D,F,G,H,I	No	---	Yes 20/
83-4 - Reproduction -	TGAI	B,D,F,G,H,I	No	---	Yes 21/

GENERIC DATA REQUIREMENTS FOR ESBIOTHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	B,D,F,G,H,I	Yes	PHES0006, PHES0008	No
84-2 - Chromosomal Aberration	TGAI	B,D,F,G,H,I	No	---	Yes 22/
84-2 - Other Mechanisms of Mutagenicity	TGAI	B,D,F,G,H,I	No	---	Yes 23/
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B,D,F,G,H,I	No	---	Yes 24/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by case basis.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C= Aquatic, Food Crop; D = Aquatic, Non-Food; E= Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.

3/ Unless otherwise specified, data must be submitted no later than six months after publication of this Standard.

4/ Esbiothrin is a mixture of Bioallethrin and Esbiol. It does not appear to be registered separately from the other two products. Therefore, it probably has a similar use pattern to Bioallethrin and Esbiol.

5/ The presently available Supplementary study may be upgraded if the data are recalculated and resubmitted.

6/ This study is not required since the test article is not an organophosphate.

7/ Subchronic feeding data need not be submitted if chronic studies in the rat are submitted. However, the Registrant should be aware that subchronic studies are useful and often necessary in determining the maximum tolerated dose (MTD) used for oncogenicity studies in rodents (mice and rats).

8/ If data are to be submitted, it must be submitted no later than 12 months after publication of this Standard.

9/ Subchronic feeding data in a nonrodent species will not be required if an acceptable chronic study in a nonrodent species is submitted.

10/ If data are to be submitted, it must be submitted no later than 12 months after publication of this Standard.

11/ Data must be submitted no later than 7 months after the publication of this Standard.
12/ A 90-day dermal study is not required for this use pattern.
13/ This requirement is reserved pending the receipt and review of the Exposure Assessment for this chemical.
14/ This study is not required because the acute toxicity study in the hen is not required. Occasionally, in this class of chemicals, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals if appropriate preservation and staining techniques are employed.
15/ The data must be submitted no later than 42 months after the publication of this Standard.
16/ The data must be submitted no later than 42 months after the publication of this Standard.
17/ The data must be submitted no later than 42 months after the publication of this Standard.
18/ The data must be submitted no later than 42 months after the publication of this Standard.
19/ The data must be submitted no later than 12 months after the publication of this Standard.
20/ The data must be submitted no later than 12 months after the publication of this Standard.
21/ The data must be submitted no later than 20 months after the publication of this Standard.
22/ The data must be submitted no later than 10 months after the publication of this Standard.
23/ The data must be submitted no later than 10 months after the publication of this Standard.
24/ The data must be submitted no later than 14 months after the publication of this Standard.

F. Toxicology Summary Tables (Continued)

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING ESBIOTHRIN

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING:				
81-1 - Acute Oral - Rat	MP	No	-	Yes
81-2 - Acute Dermal	MP	No	-	Yes
81-3 - Acute Inhalation - Rat	MP	No	-	Yes
81-4 - Eye Irritation - Rabbit	MP	No	-	Yes
81-5 - Dermal Irritation - Rabbit	MP	No	-	Yes
81-6 - Dermal Sensitization - Guinea Pig	MP	No	-	Yes

1/ Composition: MP= Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.

G. Bibliography

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PHES0006 Chantot, J.F.; Vannier, B. (1984) Esbiothrin Detection of a Mutagenic Potency With a Bacterial Test (Ames Test): Ref. RU-EBT-84.04.04/A. Unpublished study prepared by Roussel Uclaf, Romainville, France. 14 p.

PHES0007 Vannier, B.; Fournex, R. (1984) Esbiothrin: Detection of a Mutagenic Potency. Micronucleus Test in the Mouse: Ref. RU-EBT-84.603/A. Unpublished study Prepared by Roussel Uclaf, Romainville, France. 14 p.

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Chem No. 29A Bioallethrin — File Last Updated _____ — Current Date: 2/87

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral-rat/Roussel Uclaf/#RU-BA-79829/A; 11/5/79	Bioallethrin Neuville 8 L 1461; Polyethylene glycol 200	Not given	LD_{50}:709(397.9-1756.0) mg/kg (male) 1041.9(805.8-1348.7) mg/kg (female)	III	Guideline MRID: 00151444
Acute dermal-rat/Cooper Technical Bur./study # illegible; 11/71	Bioallethrin IL0686; 94% pure	Not given	LD_{50}>3200 mg/kg (diluted with 20% xylene) and 5000 (3444-7250) mg/kg undiluted in females. Inadequate reporting.	III	Supplementary MRID: 00122491
90-day feeding-rat/ Cooper Tech. Bur./# WELL BA-72.16.02/A; 2/16/72	Tech. Bioallethrin; #1017; 93% pure	Not given	LOEL 5000 ppm, NOEL 1500 ppm; decr. body wt. gain, incr. serum liver enzymes (females), incr. liver wts. (both sexes). Doses tested: 500, 1500, 5000, 10000 ppm. Core grade pending submission of histopathology tables (summary).		Supplementary MRID: 00122492
6-month feeding-dog/Int. Res.+Devel. Corp./No study #; 9/14/82	Bioallethrin OL-1243, OL0411 92.5% purity	Not given	LOEL 1000 ppm, NOEL 200 ppm; centrilobular hydropic degeneration of liver - both sexes; supporting clinical chemistry evidence. Levels tested: 0, 200, 1000, 5000 ppm.		Minimum MRID: 00151447
Teratogenicity-rat/Food + Drug Res. Labs/#FDRL-BA-79.20.04; 4/20/79	Bioallethrin L7611; Code # 108-79; 92.5%	238638	NOEL for maternal tox. 125 mg/kg/d (deaths). LOEL 195 mg/kg/day. NOEL for fetotox. could not be estab. - incr. # with rudimentary 14th ribs at all levels. NOEL terato. 195 mg/kg/d (HDT). Levels tested: 0, 50, 125, 195 mg/kg/day.		Guideline MRID: 00078624
DNA Damage/Repair-E.coli Roussel Uclaf/RU-BA-79.27.12/A; 12/27/79	Bioallethrin	252029	Growth inhibition study at the following dose levels: 125, 250 and 500 micrograms/plate. Negative results.		Acceptable MRID: 00133570

Chem No. 25A Bioallethrin — File Last Updated _____ — Current Date 1/81

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Reverse Mutation - S. typh./Roussel Uclaf/#RU-BA-79.27.12/A; 12/27/79	Bioallethrin #8L1461	252029	Tested with/without metabolic activ. conc. range: 2-5000 micrograms/plate Results negative in TA 1537, TA 1538 TA 98. Weak positive in TA 100 and TA 1535 with activation, but not statistically significant.		Acceptable MRID: 00133570
Mouse micronucleus Roussel Uclaf/#RU-BA-79.27.12/A; 12/27/79	Bioallethrin Batch 79	252029	Total doses tested: 100, 200, 400 mg/kg (males); 75, 150, 300 mg/kg (females). Administered in 2 equal doses. Results negative, however, incomplete data received.		Unacceptable MRID: 00133570
Chromosomal Aberration - Nat. Inst. Hyg. Sci., Tokyo/Mut. Res. 66: 277-290. 1979	Bioallethrin	Not given	Results reported for 0.2 ml of a 0.0019 mg/ml solution. Strongly positive. Unknown which isomer tested, however.		Unacceptable MRID: 00141594

File Last Updated _____ Current Date 9/87

Chem No. 25A Esbiol

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral - rat/Roussel Uclaf/# RU-SB-79830/A; 11/5/79	Esbiol # Neuville 7L 1193	Not given	LD_{50} 574.5 (399.6-742.1)mg/kg (male) 412.9(219.4-537.0) mg/kg (females)	II	Guideline MRID: 00151460
Eye Irrita. - rabbit/ Japan. Mosquito Coil Co. # OU-SB-75.03.22/A; 3/22/75	Esbiol	Not given	Appears to be minimal irritant, however, results not scored properly.		Supplementary MRID: 00151466
Dermal Irrita.-rat, rabbit/Shinshu U. Med. Coll SU-SB-75.07.24/A; 7/75	Esbiol	Not given	Did not appear to be dermally irritating, however, unusual test design	IV	Supplementary MRID: 00151465
90-day + 6 mo. feeding - rat/Shinshu U. Med. Coll SU-SB-75.07 19/A; 7/75	Esbiol 95% pure	Not given	No stat. sig. toxic effects noted in any treated groups. NOEL 0.3% (M) 0.15% (F). Dose levels tested: .01, .03, .1, .3 (M); .005, .01, .03, .15 (F). Insufficient histopathology.		Supplementary MRID: 00151470
Inhalation - 1 month - rat, mouse/Jap. Mosquito Coil Co./#OU-SB-75.05 27/A; 5/27/75	Esbiol	Not given	Exposed to aerosol 2 hr/day, 6 days/wk for 1 mo. Doses: 0.5%, 2.5%, 5%. Clinical signs - excitation, tail raising, salivation, trembling (2.5% + 5%). Some F mice deaths in 2.5 and 5% groups. No histopath. changes. No particle size analyses.		Supplementary MRID: 00151467
Teratology - rat/Chugai Pharmaceut. Co./#CP-SB-75 02 28/A; 2/75	Esbiol	Not given	Maternal Tox. NOEL 0.025 ml/kg based on tremors, salivation, piloerection Fetotox. NOEL 0.1 ml/kg (HDT). Teratogenic NOEL 0.1 ml/kg (HDT). Levels tested 0.025, 0.05, 0.1 ml/kg. A/D ratio: 4.		Supplementary MRID: 00151471

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - Mice/Chugai Pharmaceut. Co./#CP-SB-75.02.28/A; 2/75	Esbiol	Not given	Maternal Tox. NOEL could not be established - incr. abortion, sterility rates at all dose levels. Fetotox. + Teratogen. NOEL's 0.1 ml/kg (HDT). Levels tested: 0.05, 0.1 ml/kg. Dosages not given over entire organogenesis period.		Supplementary MRID: 00151471

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOLL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral - rat/Roussel Uclaf/#RU-EBT-79828/A 11/5/79	Esbiothrin # 9 L 1069	Not given	LD_{50} in PEG 200: 432.3(270.5-728.3) mg/kg (M); 378.0(219.3-555.6) mg/kg (F)	II	Guideline MRID: PHES0001
Acute dermal - rabbit/ Cntr. Internat. Tox., Miserey, France/#430 TAL #CIT/EBT-430-84/A; 7/27/84	Esbiothrin # 3 L 1577 93.2% pure	Not given	Acute dermal LD_{50}>2000 mg/kg	III	Guideline MRID: PHES0002
Acute inhalation - rat/ Huntingdon Res. Cntr./ # RSL 640/84470;10/16/84	Esbiothrin #3 L 1577; 93.2%	Not given	Combined LC_{50}: 2.63 g/m^3 (S.E. 0.207 g/m^3). Data needs to be re-calculated.	III	Supplementary MRID: PHES0003
Eye Irritation - rabbit/ Roussel Uclaf/# 83316; 3/9/84	Esbiothrin # 014 OL 0925	Not given	Minimally irritating to rabbit eyes. Mean score: 10	IV	Guideline MRID: PHES0004
Dermal Irrita. - rabbit/ Roussel Uclaf/#83315; 3/8/84	Esbiothrin # 014 OL 0925	Not given	Slightly irritating to rabbit skin. PIS=1.05	III	Guideline MRID: PHES0005
Reverse Mutation - S. typh./Roussel Uclaf/# RU-EBT-84.04.04/A;4/4/84	Esbiothrin # OLO 925	Not given	Levels tested: 100, 500, 1000, 5000 micrograms/plate. Negative results.		Acceptable MRID: PHES0006
Mouse Micronucleus/ Roussel Uclaf/#RU-EBT-84.603/A; 3/21/84	Esbiothrin # 3 L 1577; 93.2% pure	Not given	Negative results, however, no evidence of toxicity (clinical or cellular). Level tested: 180 mg/kg		Unacceptable MRID: PHES0007
Mammalian Cell Forward Mutation/Huntingdon Res. Cntr./# RSL 642/84422 8/1/84	Esbiothrin	Not given	Negative results. Levels tested: Without activation - 0,30,40,50,60 70,80,35,45,55 micrograms/ml. With activation - 0,45,55,65,75,85,95,60, 70,80,90,100,110,120 micrograms/ml.		Acceptable MRID: PHES0008

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

4/28/87

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - rat (81-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO: 00151444

TEST MATERIAL: Bioallethrin

SYNONYMS: d-trans Allethrin

STUDY NUMBER(S): RU-BA-79829/A

TESTING FACILITY: Roussel Uclaf Research Centre, Romainville, France

TITLE OF REPORT: Bioallethrin - Acute Oral Toxicity Study in the Rat

AUTHOR(S): L. Audegond, E. Collas and R. Glomot

REPORT ISSUED: 11/5/79

IDENTIFYING VOLUME: Vol. 1 of 5, Part 1 of 2, Tab BA-1

CONCLUSION: LD_{50} in polyethyleneglycol 200 in males : 709 (397.9-1756.0) mg/kg.
LD_{50} in polyethyleneglycol 200 in females: 1041.9 (805.8-1348.7) mg/kg.

Toxicity Category: III

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone
Description: Not given
Batch #(s), Other #(s): Neuville 8 L 1461
Purity: Not given
Source: Not given
Vehicle (if applicable): Polyethyleneglycol

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female CD 1 Spraque Dawley rat
Age: Not given
Weight(s): 100-110 grams
Source(s): IFFA CREDO breeding colony, 69210 St. Germain sur l'Arbresle, France

3. Protocol:

Ten male and ten female rats were tested per dose. Five doses were tested in males and 4 doses were tested in females. The animals were dosed by gavage with a constant volume of 10 ml per kg bodyweight. In males, 400.0, 520.0, 676.0, 878.8 and 1142.4 mg/kg test substance was administered and in females, 400.0, 729.0, 1328.6 and 2421.4 mg/kg test substance was administered. The animals were fasted overnight prior to dosing and were observed for 14 days after dosing (frequently during the day of dosing and twice daily thereafter). Bodyweights were measured on the day of dosing, weekly thereafter and at death. All animals were subjected to complete gross necropsies. The LD_{50}'s and 95% confidence intervals were calculated by the method of Finney (probit Analysis).

B. RESULTS:

Observed clinical signs included tremors, preconvulsions, epistaxis, clonic convulsions and hypermotility. According to the authors, the bodyweight gain of all rats which survived to terminal sacrifice was normal. The following table gives some of the more significant clinical signs noted during the study.

	Dose Level (Mg/kg)								
	Males					Females			
	400	520	676	878.8	1142.4	400	729	1328.6	2421.4
Lungs: Congestion	2/10			2/10	1/10				
Stomach: Congestion	1/10	2/10	3/10						
Heart: Spots of hemorrhage			1/10		3/10				1/10
Stomach: Spots of hemorrhage			1/10						
Kidneys: Pale			1/10					1/10	

The acute oral LD_{50} of Bioallethrin in polyethyleneglycol 200 in the female rat was calculated to be 1041.9 mg/kg (805.8-1348.7 mg/kg - 95% confidence interval) and the LD_{50} in the male rat was calculated to be 709.0 mg/kg (397.9-1756.0 mg/kg - 95% confidence interval).

C. DISCUSSION:

The study is adequate as written. The classification is CORE GUIDELINE.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Acute dermal - rat (81-2) TOX. CHEM. NO.: 25A

MRID NO.: 00122491

TEST MATERIAL: Bioallethrin

SYNONYMS: d-Trans Allethrin

STUDY NUMBER(S): Illegible

SPONSOR: Illegible

TESTING FACILITY: Cooper Technical Bureau, Berkhamsted

TITLE OF REPORT: Bioallethrin - Rat Dermal and Intraperitoneal Toxicity

AUTHOR(S): L.M. Wallwork and J.C. Malone

REPORT ISSUED: 11/71

CONCLUSION: LD_{50}>3200 mg/kg for bioallethrin diluted with 20% xylene and the LD_{50} was calculated to be 5000 mg/kg (3444-7250 mg/kg) when undiluted bioallethrin applied. Only females were tested.

Toxicity Category: III

Classification: CORE SUPPLEMENTARY due to inadequate reporting.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone
Description: Not given
Batch #(s), Other #(s): ILO686
Purity: 94% (w/w)
Source: Not given
Vehicle (if applicable): Xylene

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (Sexes): Female Wistar rats
Age: Not given
Weight(s): 90-110 g
Source(s): Not given

3. Procedure:

The method was that of Noakes and Sanderson (1969). No details were provided. The exposure time was 24 hours and the animals were observed an additional time of 14 days. Bioallethrin was applied either as a neat

solution or in 20% xylene. In both cases, the material was applied and covered with an occlusive dressing. When Bioallethrin was diluted with xylene, 4 rats/group were tested at the following dose levels: 800, 1600 and 3200 mg/kg. When Bioallethrin was applied neat, the following dose levels were tested: 1250, 2500, 5000 and 10000 mg/kg. LD_{50}'s were calculated by the method of Weil (1952).

RESULTS:

No animals died in the groups tested with 20% xylene. The maximum volume was applied. Signs of dermal irritation associated with the application of xylene were observed. Animals at the highest dose levels showed muscular tremors and lethargy for up to 48 hours after application. The LD_{50} was calculated to be greater than 3200 mg/kg. In the groups dose with neat bioallethrin, the following numbers of animals died following treatment:

	Dose (mg/kg)			
	1250	2500	5000	10000
No. died/No. dosed:	0/6	1/6	2/6	6/6

All deaths occurred within 48 hours of application. Rats in the 5000 mg/kg group showed signs of muscular tremors for approximately 2-3 days after application. The LD_{50} was calculated to be 5000 mg/kg (3440-7250 mg/kg).

DISCUSSION:

No details were provided on the method of application or how the animals were observed. No bodyweights were taken after the test was initiated and no details were provided concerning time of death (other than a general statement). It is unknown as to whether or not gross necropsies were performed. In addition, only one sex was tested. This study is classified as CORE SUPPLEMENTARY.

Reviewed by Pamela Hurley
Section 2 Tox Branch (TS-769C)
Secondary Reviewer Edwin Budd
Section 2 , Tox Branch (TS-769C)

82-1 (rat)

DATA EVALUATION REPORT

STUDY TYPE: 90-Day Oral - Rat (82-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO: 00122492

TEST MATERIAL: Technical Bioallethrin

SYNONYMS: d-Trans Allethrin

STUDY NUMBER(S): WELL-BA-72.16.02/A

REPORT NUMBER: 40-72

SPONSOR: The Wellcome Foundation Ltd., England

TESTING FACILITY: Cooper Technical Bureau, Berkhamsted, England

TITLE OF REPORT: Bioallethrin, rat oral 90 day toxicity study

AUTHOR(S): L.M. Wallwork, R.B. Clampitt and J.C. Malone

REPORT ISSUED: 2/16/72

IDENTIFYING VOLUME: Volume 1 of 5, Tab BA-7

CONCLUSION: NOEL 1500 ppm, LOEL 5000 ppm (decreased bodyweight gain, increased levels of liver enzymes in females, increased liver weights in both sexes. Many animals had respiratory infections.

Classification: CORE SUPPLEMENTARY until tables are provided for histopathology results.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name Technical grade bioallethrin
Description: Not given
Batch #(s) Other #(s) Batch No 1017
Purity 93%
Source Not given
Vehicle (if applicable) N/A
Positive Control(s) (if applicable) N/A

2 Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes) Carworth SPF Wistar Rats
Age Weanling
Weight(s) 50-93g
Source(s) Not given

3. Procedure:

a. Dietary Preparation (if applicable):

Frequency of preparation: Premix and treated feed prepared every 14 days. Food changed in hoppers 2X/week.
Storage conditions: Stored in dark at 4°C.
Stability Analyses: Duplicate samples taken at day 0 and stored in loosely stoppered bottle in the dark at ambient temperature (average 23°C). Further duplicate samples taken from stored material at 6, 20 and 50 days.
Homogeneity Analyses: Not done
Concentration Analyses: Not done

b. Basis For Selection of Dosage Levels:

Not reported.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered (ppm)	Interim Sacr. 45 days		Main Study 90 days	
		male	female	male	female
Contr.	0	5	5	11	11
1	500	5	5	11	11
2	1500	5	5	11	11
3	5000	5	5	11	11
4	10000	5	5	11	11

d. Procedures for Studies Other Than Feeding and/or Additions, Changes in Feeding Study: None

e. Clinical Observations and Mortality: Rats observed daily for clinical signs of toxicity. Vaginal smears prepared daily from female rats during last month of trial. Changes in cell morphology followed microscopically.

f. Body Weight Determinations: Bodyweights recorded every 7 days.

g. Food and/or Water Consumption: Food consumption recorded weekly.

h. Ophthalmological Examinations (if applicable): Not done

i. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals):
5 animals of each sex from each group killed and sampled at 45 days; all animals killed and sampled at 90 days by carbon dioxide and cardiac puncture.

The following CHECKED (X) parameters were examined:

X		X	
	Hematocrit (HCT)*		Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*		Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*		Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*	x	Packed cell volume (PCV)
	Platelet count*		
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
	Calcium*	x	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*		Cholesterol*
	Potassium*		Globulins
	Sodium*	x	Glucose*
	Enzymes:	x	Total bilirubin*
x	Alkaline phosphatase	x	Total protein* (TP)
	Cholinesterase		Triglycerides
	Creatinine phosphokinase*		
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT, GPT)*		
x	Serum aspartate aminotransferase (also SGOT, GOT)*		

3) Urinalysis:

Collection times for urine (including # of animals):
5 animals/sex/dose at 45 and 90 days; collected overnight under conditions of food and water deprivation. Composite samples.

The following CHECKED (X) parameters were examined:

X		X	
	Appearance*	x	Glucose*
	Volume*	x	Ketones*
	Specific gravity*		Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

j. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

5 animals/sex/dose sacrificed at 45 days had organ weights taken. Gross pathologic examinations were conducted on animals sacrificed at 45 days for at least the following tissues: lung, liver, thymus and kidney. It is unclear from the report whether or not complete gross pathologic examinations were conducted on these animals.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

All animals.

k. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

None of the animals sacrificed at 45 days were subjected to microscopic examination.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

All animals in the control and high dose group sacrificed at 90 days. Animals in the lower dose groups were not examined because no effects related to treatment were observed in the high dose group.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines. The (#) tissues were examined microscopically.

X	
	Digestive system
x	Tongue
x	Salivary glands*#
x	Esophagus*
x	Stomach*#
x	Duodenum*#
x	Jejunum*
x	Ileum*#
x	Cecum*#
x	Colon*#
	Rectum*
xx	Liver*#
	Gall bladder
x	Pancreas*
	Respiratory
x	Trachea*#
xx	Lung*#

X	
	Cardiovasc./Hemat.
x	Aorta*
xx	Heart*#
x	Bone marrow*#
x	Lymph nodes*#
xx	Spleen*#
xx	Thymus*#
	Urogenital
xx	Kidneys*#
x	Urinary bladder*#
xx	Testes*#
x	Epididymides#
xx	Prostate#
x	Seminal vesicle
xx	Ovaries#
xx	Uterus*#
x	Vagina

X	
	Neurologic
xx	Brain*#
x	Periph. nerve*
	Spinal cord (3 levels)*
xx	Pituitary*#
x	Eyes (optic n.)*#
	Glandular
xx	Adrenals*#
	Lacrimal gland
x	Mammary gland*
	Parathyroids*
xx	Thyroids*#
	Other
x	Bone*
x	Skeletal muscle*
x	Skin
	All gross lesions and masses

l. Statistical Analyses: The 't' test was used for comparisons between treated and control groups.

B. RESULTS:

1. Dietary Preparation: Bioallethrin was found to be stable in the diet for up to 50 days.

2. Clinical Observations and Mortality: One male rat in the 5000 ppm group showed signs of respiratory distress for 5 days during the second week of the study, but recovered. One female rat in the 1500 ppm group sustained traumatic damage to one eye during the 5th week of the study and keratitis remained until termination of the study. No clinical signs of toxicity were noted and no animals died during the study.

3. Body Weight Determinations: In male rats, animals in the 500 and 1500 ppm groups showed significant increases in body weight gain at various times throughout the study. Animals in the 5000 ppm group showed a slight but significant decrease in bodyweight gain during weeks 2 to 6, but recovered thereafter. Animals in the 10000 ppm group showed significant decreases in bodyweight, starting at week 2. In female rats, animals in the 5000 ppm group showed a slight but significant depression in bodyweight gain during weeks 4 through 8 and animals in the 10000 ppm group showed significant depressions in bodyweight gains starting at week 2.

4. Food and/or Water Consumption: No changes in food consumption were noted at any of the dose levels. There appeared to be no significant differences in food efficiency between control and treated groups in both males and females, although during the latter stages of the study, there was considerable fluctuation in both treated and control groups.

5. Ophthalmological Examinations: Not done.

6. Estrous Cycle: No significant differences were noted in the length of the estrous cycle between treated and control groups.

7. Hematology: In male rats at 45 days, a significant decrease in hemoglobin was observed at all dose levels. However, by 90 days these decreases had disappeared (a second group of animals). Statistically significant decreases in packed cell volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were also observed in some groups, but the decreases were not generally beyond 10% of the control values.

8. Clinical Chemistry: The results indicated a significant increase in blood glucose in both the 5000 and 10000 ppm dose levels at 45 days (females). The other two dose levels showed an increase, but they were not significant. At 90 days, statistically significant increases in GOT, GPT and TP levels in females were observed in both the 5000 and 10000 ppm dose levels. These changes indicate possible slight liver dysfunction.

9. Urinalysis: Urinalysis indicated proteinurea in both males and females at both 45 and 90 days at dose levels of 1500 ppm and above. The authors of the report considered the increases to be biologically insignificant.

10. Gross Pathology: Gross examinations did not reveal any compound related effects. Sporatic incidences of cystic and hydronephrotic kidneys were observed in both control and treated animals.

11. Organ Weights: Measurements of organ weights indicated increases in liver weights in both males and females at 45 days (males: 1500 ppm (relative), 5000 and 10000 ppm (relative and absolute); females: 5000 and 10000 ppm (relative)) and at 90 days (males: 500 ppm (absolute), 5000 and 10000 ppm (relative and absolute); females: 5000 and 10000 ppm (relative and absolute)). Decreases in ovary weights were noted at 45 days (1500 ppm (relative and absolute), 10000 ppm (relative and absolute)) and decreases in spleen weights in males were noted at 90 days (500 ppm (relative), 1500 ppm (relative and absolute), 5000 ppm (relative and absolute)). At 10000 ppm the mean absolute weights were 83% of controls, but were not considered to be statistically significant. Finally, a slight to moderate increase in the mean uterus weights were seen in the 1500 ppm (absolute and relative) and 10000 ppm (relative) groups at 90 days.

12. Histopathology:

    a. Nonneoplastic lesions: No compound-related effects were observed during the histopathological examination of any of the treated animals when compared to the controls. Congestion and chronic interstitial pneumonitis were noted in the majority of the animals, including controls. Some of these animals were also observed to have "patchy bronchopneumonia, consolidation and minimal peribronchiolar lymphoid hyperplasia". Livers of a few animals from all groups were observed to have "minimal biliary hyperplasia, chronic inflammatory cell infiltration of portal tracts and minimal deposition of fat". No tables were supplied with the report in order to verify the summaries provided. Only individual histopathology reports on each animal were provided.

    b. Neoplastic lesions: There was no indication of any neoplastic development in this study.

13. Quality Assurance Measures: This study was conducted prior to the issuance of the Good Laboratory Practice Procedures. It has no quality assurance statement.

C. DISCUSSION:

In general, the study was conducted fairly completely. There were a few items missing that are suggested in the Guidelines. These are: measurements of electrolytes in the clinical chemistry studies and ophthalmological examinations. The absence of these items are not likely to seriously affect the validity of the study. However, there was one item missing that is necessary for completion of the review. No summary tables were provided for the histopathology results. These are necessary in order to validate the summary given. The tables should contain the number of tissues examined and the number ot lesions observed for each tissue examined. Therefore, this study is considered to be CORE SUPPLEMENTARY until the tables can be provided. The NOEL for this study was observed to be 1500 ppm based upon a decrease in bodyweight gain, increased levels of liver enzymes in females and increased liver weights at 90 days in both sexes. The LOEL was 5000 ppm. It should be noted that in females sacrificed at 45 days, the mean liver weights were significantly greater than controls in the 1500 ppm and above groups. It should also be noted that the pathology results indicate that many of these animals had chronic respiratory infections.

Reviewed by: Pamela Hurley
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4/23/87

DATA EVALUATION REPORT

STUDY TYPE: 6-Month dog - oral (83-1)

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given

MRID NO: 00151447

TEST MATERIAL: Bioallethrin

SYNONYMS: d-trans Allethrin

STUDY NUMBER(S): Not given

SPONSOR: Roussel Uclaf, Romainville, France

TESTING FACILITY: International Research + Development Corporation, Mattawan, Michigan

TITLE OF REPORT: 6-Month Dietary Toxicity Study in Dogs

AUTHOR(S): L.M.P. Griggs, N.D. Jefferson and M. Blair

REPORT ISSUED: 9/14/82

IDENTIFYING VOLUME: Allethrin Data Call-In; Vol. 2 of 5; Tab BA-8

CONCLUSION: NOEL 200 ppm, LOEL 1000 ppm based upon centrilobular hydropic degeneration of the liver in males and females. Supporting evidence in clinical chemistry.

Classification: CORE MINIMUM because it is a six-month study which was acceptable as a chronic dog study at the time that it was conducted.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone
Description: clear orange slightly viscous liquid
Batch #(s), Other #(s): OL-1243 and OL 0411 (2 shipments)
Purity: 92.5%
Source: Roussel UCLAF, Romainville, France

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Beagle dogs, males and females
Age: 3-4 months and quarantined for 4 weeks
Weight(s): 5.8-12.4 kg (males), 3.6-10.4 kg (females)
Source(s): Ridglan Farms, Inc., Mt. Horeb, Wisconsin

3. Procedure:

a. Dietary Preparation (if applicable):

Bioallethrin added to 5000 g of diet and mixed for 5 minutes. This was then added to diet being prepared and mixed for 30 minutes.

Frequency of preparation: Weekly

Storage conditions: Not stated

Stability Analyses: Conducted at week 1. Stored for 10 days and analyzed for test article concentration.

Homogeneity Analyses: Samples collected from top, middle and bottom of blender following 10, 20 and 30 minute mixing intervals and analyzed for test article concentration.

Concentration Analyses: Duplicate samples from each treatment group and control group were collected at 2, 3, 4, 8, 13 and 26 weeks of study and analyzed for test article concentration.

b. Basis For Selection of Dosage Levels:

Dose selection was made on the basis of a 2 week range-finding study in which 1 animal/sex/dose was administered the following dose levels: 0, 1000, 2000, 4000 or 8000 ppm.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered ppm	Main Study 6 months	
		male	female
Contr.	0	6	6
1	200	6	6
2	1000	6	6
3	5000	6	6

d. Clinical Observations and Mortality:

The animals were observed daily for general physical appearance and behavior, pharmacologic and toxic signs, moribundity and mortality.

e. Body Weight Determinations:

Individual body weights were recorded weekly, beginning with the pretest period.

f. Food and/or Water Consumption:

Individual food consumption was recorded weekly, including one week prior to study initiation.

g. Ophthalmological Examinations (if applicable):

Ophthalmoscopic examinations were performed by a veterinary ophthalmologist for all dogs during the pretest period, and at 3 and 6 months of the study.

h. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals):
During pretest period and at 1, 2, 3, 4, 5 and 6 months of the study (all dogs).

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*	x	Reticulocyte count
x	Platelet count*		
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
x	Phosphorus*	x	Cholesterol*
x	Potassium*	x	Globulins (calculated)
x	Sodium*	x	Glucose*
	Enzymes:	x	Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase		Triglycerides
	Creatinine phosphokinase*	x	Uric acid
x	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
x	Gamma glutamyl transpeptidase		

3) Urinalysis:

Collection times for urine (including # of animals):

All animals during pretest period and at 2, 4, and 6 months of the study.

The following CHECKED (X) parameters were examined:

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*	X	Nitrites
X	Protein*	X	Urobilinogen

i. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

None

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

j. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

None.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

All animals.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X	Digestive system
	Tongue
x	Salivary glands*
x	Esophagus*
x	Stomach*
x	Duodenum*
x	Jejunum*
x	Ileum*
x	Cecum*
x	Colon*
x	Rectum*
xx	Liver*
x	Gall bladder*
x	Pancreas*
	Respiratory
x	Trachea*
x	Lung* with bronchi

X	Cardiovasc./Hemat.
x	Aorta*
xx	Heart*
x	Bone marrow*
x	Lymph nodes*
x	Spleen*
xx	Thymus*
	Urogenital
xx	Kidneys*
x	Urinary bladder*
xx	Testes*
	Epididymides
x	Prostate
	Seminal vesicle
xx	Ovaries
x	Uterus*

X	Neurologic
x	Brain*
x	Periph. nerve* (3 types)
x	Spinal cord (3 levels)*
xx	Pituitary*
x	Eyes (optic n.)*
	Glandular
xx	Adrenals*
	Lacrimal gland
x	Mammary gland*
xx	Parathyroids*
xx	Thyroids*
	Other
	Bone*
x	Skeletal muscle*
x	Skin
x	All gross lesions and masses

k. Statistical Analyses:

Body weights, clinical chemistry tests and organ weights were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances). Dunnett's multiple comparison tables were used to judge significance of differences.

B. RESULTS:

1. Dietary Preparation: The dietary mixtures were found to be homogeneous. However, the mean test article concentration for the 200 ppm level was low (69% of the target value). The compound was stable in tests up to 10 days of storage. In periodic analyses, the average test article concentrations were within the range of 87-95% with the exception of week 1 in which the values were 69, 86 and 95% respectively for 200, 1000 and 5000 ppm, respectively.

2. Clinical Observations and Mortality: There were no mortalities during the study. Clinical observations included general body trembling and slight irregular heart rhythms at the 5000 ppm level. In males, there was also excessive salivation at the highest dose level. Other clinical findings were observed in all groups, including controls.

3. Body Weight Determinations: Statistically significant decreases in body weight gain were observed in both sexes at the 5000 ppm level and in males at the 1000 ppm level. However, the differences in actual body weights between the treated and control groups were not statistically significant when measured at 13 and 26 weeks (although at the 5000 ppm level, the males weighed 14% and 15% less than the controls at 13 and 26 weeks, respectively).

4. Food and/or Water Consumption: At the 5000 ppm level there was a consistent decrease in food consumption in both sexes. Slight decreases in food consumption were noted at the 200 ppm level and sporatic fluctuations in food consumption were noted at the 1000 ppm level.

5. Ophthalmological Examinations: No compound-related effects were observed during the ophthalmological examinations.

6. Hematology: Sporatic changes were noted, particularly in the high dose group but nothing appeared to be either consistent or biologically significant.

7. Clinical Chemistry: Increases in alkaline phosphatase (AP) were observed in the 5000 ppm groups (both sexes) and in the 1000 ppm group (males). Alanine aminotransferase (SGPT) was also increased in both sexes at the 5000 ppm level. Statistically significant increases in gamma glutamyl transpeptidase (GGTP) and aspartate aminotransferase (SGOT) were also noted at the highest dose level, but the increases were small and were thus probably not biologically significant (see Tables Ia and Ib).

Table Ia
Mean, Standard Deviation, N and Significance of Biochemical Values

Males

Parameter		0 ppm $\bar{x}$	S.D.	N	200 ppm $\bar{x}$	S.D.	N	1000 ppm $\bar{x}$	S.D.	N	5000 ppm $\bar{x}$	S.D.	N
Alkaline Phosphatase IU/l	Pretest	67	13.8	6	69	5.9	6	76	4.5	6	68	10.2	6
	1	46	9.3	6	51	11.8	6	60*	3.7	6	98	54.4	6
	2	39	9.8	6	41	6.0	6	51*	3.6	6	125*	67.2	6
	3	38	9.8	6	39	6.0	6	52*	10.5	6	124*	47.3	6
	4	32	10.3	6	33	9.7	6	45*	8.6	6	136*	59.1	6
	5	29	6.9	6	28	6.3	6	51**	10.9	6	131*	53.9	6
	6	29	8.2	6	30	7.4	6	57*	20.3	6	143*	59.0	6
Alanine aminotransferase (SGPT) IU/l	Pretest	34	4.3	6	32	4.3	6	35	6.3	6	33	4.3	6
	1	33	11.2	6	38	5.0	6	36	3.4	6	75**	21.2	6
	2	26	2.7	6	25	3.2	6	26	3.4	6	67**	29.6	6
	3	36	4.2	6	35	5.3	6	33	4.6	6	94**	31.8	6
	4	32	5.2	6	31	4.8	6	32	6.3	6	85**	29.9	6
	5	29	3.6	6	28	4.2	6	28	7.4*	6	88**	25.0	6
	6	27	4.1	6	28	5.9	6	28	5.8	6	99**	31.4	6
Aspartate aminotransferase (SGOT) IU/l	Pretest	25	3.9	6	22	1.5	6	27	4.4	6	23	3.0	6
	1	29	9.9	6	28	10.5	6	26	4.2	6	27	4.8	6
	2	16	2.8	6	17	1.2	6	18	2.7	6	19	2.9	6
	3	25	3.8	6	21	2.2	6	24	3.1	6	24	3.3	6
	4	24	5.1	6	19	2.1	6	23	4.8	6	23	2.6	6
	5	21	5.0	6	16*	1.0	6	18	3.6	6	20	2.7	6
	6	17	3.7	6	14	2.0	6	17	3.7	6	21*	2.1	6
Gamma glutamyl transpeptidase (GGTP)	Pretest	3	1.2	6	3	1.1	6	4	1.8	6	4	1.8	6
	1	6	0.8	6	5	1.0	6	5	0.8	6	6	1.0	6
	2	3	1.4	6	4	1.0	6	4	0.8	6	4	1.2	6
	3	2	0.8	6	3	1.0	6	3	1.0	6	4*	1.2	6
	4	5	0.5	6	5	0.8	6	5	1.2	6	7*	1.7	6
	5	4	0.8	6	5	0.8	6	6	1.0	6	7**	0.8	6
	6	4	0.8	6	4	0.9	6	4	1.0	6	6**	0.5	6

*Significantly different from control group mean; $p < 0.05$
** Significantly different from control group mean; $p < 0.01$

$\bar{x}$ - Mean
S.D. - Standard deviation
N - Number of observations

Table Ib
Mean, Standard Deviation, N and Significance of Biochemical Values

Females

Parameter		0 ppm $\bar{x}$	S.D.	N	200 ppm $\bar{x}$	S.D.	N	1000 ppm $\bar{x}$	S.D.	N	5000 ppm $\bar{x}$	S.D.	N
Alkaline Phosphatase IU/l	Pretest	76	20.9	6	63	13.0	6	71	18.4	6	69	10.2	6
	1	53	12.0	6	46	7.3	6	59	19.1	6	129**	54.4	6
	2	48	12.5	6	38	8.1	6	51	17.6	6	137**	67.2	6
	3	46	12.5	6	35	9.2	6	54	14.4	6	158**	47.3	6
	4	40	14.3	6	28	8.6	6	44	13.0	6	124**	59.1	6
	5	34	13.6	6	27	6.9	6	44	10.6	6	130**	53.9	6
	6	41	23.2	6	30	12.6	6	51	21.6	6	132**	59.0	6
Alanine aminotransferase (SGPT) IU/l	Pretest	35	8.7	6	30	4.2	6	30	6.0	6	35	3.9	6
	1	40	8.4	6	34	3.1	6	31	5.0	6	130**	39.8	6
	2	29	6.2	6	24	2.3	6	23	4.7	6	86*	34.5	6
	3	42	13.1	6	30	3.6	6	30	6.6	6	129**	34.9	6
	4	33	9.4	6	28	3.3	6	27	5.7	6	133**	60.0	6
	5	28	6.3	6	25	3.3	6	24	6.1	6	137**	50.3	6
	6	27	9.2	6	25	4.6	6	23	6.3	6	122**	31.9	6
Aspartate aminotransferase (SGOT) IU/l	Pretest	26	1.7	6	26	5.5	6	25	4.9	6	27	4.0	6
	1	29	6.5	6	28	3.9	6	28	4.7	6	35	5.5	6
	2	18	1.0	6	19	3.8	6	17	1.9	6	22*	3.5	6
	3	27	8.5	6	25	3.5	6	22	3.1	6	33	14.2	6
	4	24	2.5	6	22	4.6	6	21	4.5	6	30	7.1	6
	5	18	2.5	6	18	3.7	6	16	3.1	6	21**	3.5	6
	6	16	1.0	6	22	10.4	6	16	1.8	6	22**	3.1	6
Gamma glutamyl transpeptidase (GGTP)	Pretest	1	0.0	6	1[a]	0.4	6	1[a]	0.4	6	1[a]	0.5	6
	1	5	0.8	6	5	0.5	6	5	0.8	6	7	1.4	6
	2	3	1.0	6	3	0.8	6	3	0.8	6	4	1.8	6
	3	2[a]	0.8	6	2[a]	1.0	6	3	1.0	6	4**	1.8	6
	4	6	1.0	6	4	0.8	6	5	1.5	6	8*	1.9	6
	5	5	0.5	6	5	1.0	6	5	0.6	6	8**	1.6	6
	6	4	0.4	6	4	0.6	6	5	0.5	6	6**	0.9	6

*Significantly different from control group mean; $p < 0.05$
** Significantly different from control group mean; $p < 0.01$

$\bar{x}$ - Mean
S.D. - Standard deviation
N - Number of observations
a - This mean includes values with a < sign.

8. Urinalysis: No compound-related changes were noted.

9. Gross Pathology: No compound-related changes were noted.

10. Organ Weights: No obvious compound-related changes were noted. However, there were equivocal compound-related increases in the mean relative liver weights in both sexes at both the 1000 and 5000 ppm levels. The authors of the report stated, "it is possible that the toxicological significance of the liver weight differences was masked by a remarkable decrease in body weight gain among animals of the 5000 ppm group." In addition to the equivocal changes in liver weight, a statistically significant decrease in the absolute weight of the heart in males was observed at the highest dose level. The toxicological significance of this is unknown.

11. Histopathology:

a. Nonneoplastic lesions: Hepatocellular degeneration of the liver was observed in both sexes at both the 1000 and 5000 ppm levels (see Table II). The response increased with increasing dose. There was acute cellular swelling which was generally centrilobular, but was also more generalized in the most severe cases. In addition, a brown granular pigment was present multifocally in the midzonal regions of the hepatic lobules (it was present both intracellularly as well as intracanalicularly). A similar brown pigment was also present within the tubular epithelial cells of the kidney. The exact nature of the pigment could not be determined, although special staining techniques were used.

Table II
Compound-Related Nonneoplastic Lesions

	Control		200 ppm		1000 ppm		5000 ppm	
	M	F	M	F	M	F	M	F
Liver								
Degeneration	0	0	0	0	2	1	6	6
Mild							1	
Moderate					2	1	4	6
Severe							1	
Brown pigment	0	0	0	0	3	1	6	6
Trace						1		
Mild					3			
Moderate							3	3
Severe							3	3
Kidney								
Pigmentation	0	0	0	0	2	0	4	3
Trace					2		2	1
Mild							2	2

b. Neoplastic lesions: No compound-related neoplastic lesions were observed.

12. Quality Assurance Measures: Multiple quality assurance inspections were conducted. The report was signed and included a statement that the study was conducted according to the FDA's Good Laboratory Practices Regulations.

C. DISCUSSION: This study generally follows what is recommended in the EPA Testing Guidelines. However, since the study was conducted during the time when 6-month dog studies were acceptable as chronic studies, the study will be accepted but will only be classified as CORE MINIMUM. The NOEL is 200 ppm and the LOEL is 1000 ppm, based upon hepatocellular degeneration of the liver in both sexes.

eviewed by: Pamela Hurley
ection 2 , Tox. Branch (TS-769C)
econdary Reviewer: Edwin Budd
ection 2 , Tox. Branch (TS-769C)

Budd 4/23/87

83-3 (rat)

DATA EVALUATION REPORT

STUDY TYPE: Teratology - rats (83-3)

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: 238638

MRID NO.: 00078624

TEST MATERIAL: Bioallethrin

SYNONYMS: d-trans Allethrin

REPORT NUMBER: FDRL-BA-79.20.04

SPONSOR: McLaughlin Gormley King Co., Minneapolis, MN

TESTING FACILITY: Food and Drug Research Laboratories, Inc.; Lab # 6059

TITLE OF REPORT: Teratologic Evaluation of d-trans Allethrin in Sprague-Dawley Rats

AUTHOR(S): M. Knickerbocker and T.A. Re

REPORT ISSUED: April 20, 1979

IDENTIFYING VOLUME: Volume 2 of 5, Tab BA-10

CONCLUSION: This study was reviewed by J. Doherty (Memo dated 10/17/79, see attached). The reviewer agrees with the conclusion given at that time. Additions to the review are given on the succeeding page(s). It was concluded that d-trans Allethrin was not a teratogen in rats at the dose levels tested. The NOEL for fetotoxicity could not be established because of the increased number of fetuses with rudimentary 14th ribs at all dose levels tested. Maternal NOEL 125 mg/kg/day.

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (46.5:46.5)
Description: clear, amber-colored liquid
Batch #(s), Other #(s): L7611; Code No. 108-79
Purity: 92.5%
Source: McLaughlin Gormley King Co.
Vehicle (if applicable): corn oil
Positive Control(s) (if applicable): aspirin

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female Sprague-Dawley (BLU: (SD) BR) rats

Age: Sexually mature
Weight(s): 230-250 g (females on day 0)
Source(s): Blue Spruce Farms, Inc., Altamont, N.Y.

Additions to the previously submitted review:

1. Procedures:

The level, 195 mg/kg/day was added after initiation of the study because the 300 mg/kg/day level was terminated due to excessive toxicity. The vehicle control, corn oil was administered at a level of 10 ml/kg/day, the volume administered to the animals treated with the test chemical. The positive control, aspirin, was administered as an aqueous suspension. When the dams were sacrificed on day 20, the urogenital tract of each was examined for anatomical abnormalities as well. In addition, those dams which died prior to termination were weighed and subjected to a thorough uterine examination. Body weights of the dams were recorded on days 0, 6, 9, 12, 15 and 20 of gestation. All animals were observed daily for clinical signs of toxicity. At the time of sacrifice (or if the animal died or was sacrificed in moribund condition), the following observations were recorded: number of corpora lutea, implantation sites, resorption sites, live and dead fetuses, sex of fetuses and body weights of fetuses. If possible, late resorptions were weighed and sexed. All fetuses were examined grossly for external abnormalities and one-third of the fetuses from each litter were given detailed visceral examinations using the Wilson free-hand technique. The remaining fetuses were prepared and examined for skeletal abnormalities.

2. Results:

Significantly reduced body weight gains in the dams and significantly reduced fetal weights were observed in the aspirin-treated animals. The fetuses from the aspirin-treated groups also exhibited several skeletal as well as soft tissue abnormalities.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE October 4, 1979

SUBJECT: EPA File No. 1021-1060, D-Trans Allethrin: teratogenic evaluation. CASWELL #25A

FROM John Doherty 10/17/79 Budd 10/17/79
Toxicology Branch/HED (TS-769)

TO Franklin Gee
Product Manager#17/RD (TS-767)

Conclusion:

The teratology study in rats has been reviewed and it is concluded that d-trans allethrin is not a teratogen in rats at doses as high as 195 mg/kg/ day (highest level tested).

However, at all test levels there was a significantly increased number of fetuses with rudimentary 14th ribs. This is considered a possible fetotoxic effect and no NOEL is established for this effect.

Toxicology Branch requests information on the detailed history of this lesion (rudimentary 14th ribs) in the strain of rats used for this study to determine if this effect is allethrin dependent.

Teratologic Evaluation of D-Trans Allethrin in Sprague Dawley Rats.

Food and Drug Research Laboratories, April 20, 1979, Lab. No. 6059. (In EPA accession No. 238638)

6 groups of female rats (28-34 per group) were used in this experiment. The doses of d-trans allethrin (92.5%) used were 50, 125, 195 and 300 mg/kg/day. The group receiving 300 mg/kg/day was terminated after the first few doses because this dose was lethal to the dams. Vehicle control and positive control (aspirin, 250 mg/kg/day) groups were also run.

The dams were impregnagted and treated by gavage on days 6-15 of gestation. The rats were sacrificed on day 20 and the uterine contents and the pups subjected to thorough examination.

Results (for controls, 50, 125 and 195 mg/kg/day d-trans allethrin)

1) The dams gained weight normally and were reported as not having changes in general appearance and behavior. There were 6 deaths in the high dose group (195 mg/kg).

2) There were no differences in pregnancy, implantation, numbers of dead or live fetuses, or number of resorption sites/dam reported.

3) There were no reported soft tissue anomalies in fetuses from d-trans allethrin treated dams.

4) The single statistically significant abnormality reported for skeletal development was a significant increase in the % of litters with rudimentary 14th ribs at all doses of d-trans allethrin tested.

		D-Trans Allethrin		
Vehicle Control	Aspirin	50 mg/kg	125 mg/kg	195 mg/kg
10/5	58/17*	18/10*	38/19*	34/15*

upper = number of fetuses affected.
lower = number of litters affected.
* significantly different from control.

There was also an increased incidence of incomplete ossification of the vertebrae at all levels of d-trans allethrin, but this was not statistically significant.

This is a CORE-GUIDELINES study.

TOX/HED:th:RD Initial EBUDD:9-21-79 Rewrite:Budd:sb:10/5/79

iewed by: Pamela Hurley
tion 2 , Tox. Branch (TS-769C)
ondary Reviewer: Edwin Budd
tion 2 , Tox. Branch (TS-769C)

Edd 4/23/87

84-2
Chinese Hamster

DATA EVALUATION REPORT

STUDY TYPE: Chromosomal Aberration - CHL cells (84-2)

TOX. CHEM. NO.: 25 or 25A

ACCESSION NUMBER: Not given

MRID NO.: 00141594

TEST MATERIAL: Allethrin

SYNONYMS: Not sure which isomer this is

REPORT NUMBER: Mutation Research 66: 277-290. 1979

TESTING FACILITY: National Inst. of Hygienic Science, Tokyo, Japan

TITLE OF REPORT: Chromosomal Aberration Tests on 29 Chemicals Combined with S-9 Mix In Vitro

AUTHOR(S): A. Matsuoka, M. Hayashi and M. Ishidate

REPORT ISSUED: Sept. 15, 1978

CONCLUSION: This study was reviewed earlier (see memo from M. Sochard to A. Heyward (8/7/85). The present reviewer agrees with the conclusions of the previous reviewer (see additional comments below).

Classification: UNACCEPTABLE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: Allethrin (isomer ratios not given).
Description: Not given
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Either ethanol, DMSO or saline

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes): Chinese hamster lung cells

Additional Comments

There are other problems with this study that render it impossible to use as a chromosomal aberration study for bioallethrin. First of all, the authors stated that allethrin was tested. Technical Allethrin is different from technical Bioallethrin. No distinction was made. On this basis alone, the study is unusable without further identification of the test chemical. No purities were given either. The vehicle used was unclear. It was one of 3 choices mentioned in the script of the report. The study should be repeated, especially since the results were positive.

CASWELL FILE

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

AUG 7 1985 005596

MEMORANDUM

SUBJECT: 1021-1217. d-trans allethrin (Bioallethrin)
Mutagenicity Assays

Tox. Chem. No. 25A
(Related are Nos. 670, 613, 77A)

FROM: M. R. Sochard, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: A. Heyward, PM Team #17
Registration Division (TS-767)

THRU: E. R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant

McLaughlin Gorman King Company
8810 Tenth Avenue N.
Minneapolis, MN 55427

Matsuoka, A.; Hayashi, M.; Ishidate, M. Jr. (1979) Chromosomal Aberration Tests on 29 Chemicals Combined with S-9 In Vitro. Mutation Research, 66:277-290. Submitted as part of Accession No. 252029.

Protocol:

A group of 29 chemicals which included allethrin, was assayed in CHL cells (chinese hamster lung cells) following treatment with S-9 mix. Test chemicals were assayed at three different doses of each, with cell cultures and chemicals incubated with shaking at 37 °C for 3 hours. Cells were then cultured in 6-cm culture dishes for 24 hours longer. Cells were colcemid treated, prepared for microscopic examination on microscope slides, and stained with Giemsa stain. One hundred well spread metaphases were counted. Chromosome aberrations were classified as follows: chromatid gaps, chromatic breaks, chromatid or chromosomal exchanges, ring formation and fragmentation, or pulverization of chromosomes. Polyploidy was also sought and recorded. Results were recorded as negative if less than 4.9 percent aberrations were seen including at high doses tested even if at sublethal concentrations.

A (+) was assigned to aberrations between 5.0 and 9.9 percent (suspicious). A positive was assigned if aberrations were at 10 to 19.7 percent (+); 20 to 49.9 percent (++) and more than 50 percent was assigned (+++). Controls included untreated and

Results:

In the above syster, with S-9 mix, allethrin was a strong positive (+++); at the 77 percent level, with chromatid gaps, chromatid breaks, chromatic or chromosome exchanges, fragmentation pulverization of chromosomes and ring formation seen at a dose-level of 0.0019 mg/ml (no other dose level results given). The conclusion was that under the circumstances reported, allethrin is mutagenic with S-9 mix. Since results are reported only for one dose level of allethrin, the study is considered unacceptable for regulatory purposes.

Core Category - Not acceptable.

ewed by: Pamela Hurley
ion 2 , Tox. Branch (TS-769C)
ndary Reviewer: Edwin Budd
ion 2 , Tox. Branch (TS-769C)

Budd 4/23/87

84-2
S. typh.
E. coli
Mouse

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity (84-2) - Growth Inhibition in E. Coli, Reverse Mutation in S. typhimurium and Mouse Micronucleus

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: 252029 MRID NO.: 00133570

TEST MATERIAL: Bioallethrin

SYNONYMS: d-trans Allethrin

REPORT NUMBER: RU-BA-79.27.12/A

SPONSOR: Roussel Uclaf, Romainville, France

TESTING FACILITY: Centre de Recherches, Roussel Uclaf, Romainville, France

TITLE OF REPORT: Detection of a Mutagenic Potency of Bioallethrin

AUTHOR(S): M. Peyre, J.F. Chantot, L. Penasse, B. Vannier and R. Glomot

REPORT ISSUED: December 27, 1979

IDENTIFYING VOLUME: Volume 2 of 5, Tab BA-9

CONCLUSION: These 3 studies were reviewed previously (see memo from M. Sochard to A. Heyward (attached)). This reviewer agrees with the conclusions reached for two of the studies, but disagrees with the conclusions reached on the mouse micronucleus study. The studies indicate that under the specified conditions for microbial assays, The E. Coli DNA damage and repair tests and the Salmonella Ames tests for forward mutation were negative for Bioallethrin. However, Salmonella strains TA100 and TA1535 gave weak but positive results with metabolic activation. The mouse micronucleus assay was negative under the conditions of the bioassay.

Classification: The Ames study and the DNA damage and repair test were ACCEPTABLE but the mouse micronucleus test was UNACCEPTABLE unless additional data can be submitted (see comments on next page).

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (46.5:46.5)
Description: Not given (solid?)
Batch #(s), Other #(s): 8L1461 (Ames), H 3565 batch 79 (mouse micronucleus)
E. coli assay - not given
Purity: Not given
Source: Not given

Vehicle (if applicable): DMSO (Ames and E. coli); sesame oil (micronucleus)

Positive Control(s) (if applicable): N-methyl N'-nitro-N-nitrosoguanidine (MNNG) (E. coli); 2-Aminoanthracene, MNNG, 9-Aminoacridine, 2-nitrofluorene (Ames); Triethylene melamine (TEM) (mouse micronucleus).

Comments:

This reviewer disagrees with the conclusion of the previous reviewer on the mouse micronucleus assay. There are three problems with the assay. First of all, TEM was administered i.p.. As a positive control, it should have been administered orally, as bioallethrin was administered. Secondly, there is some confusion concerning the dosage levels administered. Since no toxicity was observed, were these animals the same strain as those for which the LD_{50} was reported? It should have been stated as such. Thirdly, there was no evidence of toxicity, either clinical signs with the animals or cytotoxicity. The study cannot be properly evaluated without submission of additional data (if available). The data needed are:

1. Data concerning the ratio of PCE's to normochromatic erythrocytes, or some other indication of possible toxicity.

2. The strain of mouse in the quoted LD_{50} study.

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

AUG 7 1985 004596

MEMORANDUM

SUBJECT: 1021-1217. d-trans allethrin (Bioallethrin)
Mutagenicity Assays

Tox. Chem. No. 25A
(Related are Nos. 670, 613, 77A)

FROM: M. R. Sochard, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: A. Heyward, PM Team #17
Registration Division (TS-767)

THRU: E. R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant

McLaughlin Gorman King Company
8810 Tenth Avenue N.
Minneapolis, MN 55427

Peyre, M. et al. Dated November 28, 1979, Unpublished. Detection of a Mutagenic Potency of Bioallethrin. Roussel Uclaf. (36 pages, Microbial Assays as Well as Micronucleus Test in Mice).

The Peyre et al. studies indicate that under the specified conditions for the microbial assays, the E. coli DNA damage and repair tests and the Salmonella Ames tests for forward mutations were negative for bioallethrin. However, Salmonella strains TA100 and TA1535 gave weak but positive results when metabolic activation (S-9 mix) was included in the assay. Both microbial assays were Core Category - Acceptable.

The Peyre et al. mouse micronucleus assay showed bioallethrin was [illegible]tive for micronuclei induction in bone marrow of mice [illegible]inistered the chemical at levels up to a lethal dose.

Core Category: Acceptable.

Detection of a Mutagenic Potency of BioAllethrin. 1. Microbial Assays. 2. Micronucleus test in Mouse. Peyre, M.; Chantot, J.F.; Penasse, L.; Vannier B.; Glomot, R. Romainville, December 27, 1979. 36 pages. Accession No. 252029.

Protocol:

A. Microbial Assays

a. E. coli Assays, Using Bioallethrin (Batch no. 8L1461)

Growth inhibition by allethrin was compared using wild type E. coli and three mutant strains derived from the wild type which are deficient in certain repair mechanisms. E. coli strains, auxotrophic for tryptophan (trp^-) with varying proficiency in DNA repair mechanisms were compared as matched pairs for inhibition tests with test chemical. Thus, strain WP_2 derived from the wild type and having the genome trp^-, $uvra^+$, exr^+ is unable to grow without tryptophan; and proficient at excision DNA repair and is free of error-prone rec-dependent DNA repair. Its counterpart is strain CM611, trp^-, $uvra^-$ and $exrA^-$, deficient in excision-repair of DNA and has the defect error-prone, rec-dependent DNA repair. E. coli strain WP_2, thy^- and pol A^+ is unable to grow without thymine and tryptophan, but is proficient for DNA polymerase I.

Its counterpart is E. coli strain p3478 which is auxotrophic for trp^- and thy^- and in addition, is deficient in DNA polymerase I. The assay was done as follows: Dilutions of allethrin at 1250, 2500, and 5000 µg/ml were placed in wells cut into agar plates which were inoculated with bacteria so as to obtain confluent growth. As the chemical diffused through the agar it contacted the bacteria, and growth inhibition was measured, following incubation of the cultures for 18 hours at 37 °C. The positive control, N-methyl N'-nitro-N-nitrosoguanidine (MNNG) should give growth inhibition ratios between the paired E. coli greater than 1.0. The control antibiotic (chloramphenicol) should provide paired ratios of 1.0. A solvent control (DMSO) was included.

b. Salmonella Assays

Bioallethrin was tested with and without MA (metabolic activation with S-9 mix) in concentrations ranging [illegible] 2 to 5,000 µg per plate. Mutant bacteria were genetically constructed so that each strain had a different genetic defect within a genome which can be reverted to the wild type by a single mutation. A chemical-induced mutation (reversion) in any or all strains indicates a specific genetic event. (Dilutions of Bioallethrin in DMSO (solvent) were easily precipitated in culture medium at concentrations of 200 µg per plate and above.) For the test, agar plates with minimal medium were overlaid with soft agar containing admixtures of

selected diluted test chemical, selected Salmonella bacteria, with or without S-9 mix; separate plates were prepared to provide positive, negative, or vehicle (DMSO) controls. Four agar plates were prepared for each dilution per assay and data obtained were analyzed using statistical methods. Salmonella strains used were TA1535, TA100, TA1537, TA1538, and TA98.

F. Micronucleus Assay

This test is based on observations that chromosome damage may be assessed from the number of polychromatic erythrocytes in excess of normal in bone marrow of animals exposed to test chemicals. Polychromatic cells (stained blue with Giemsa stain) are normally few in number, found in marrow, and represent those erythrocytes which have not yet extruded their nuclei (normally, such cells extrude their nuclei and are recognized as non-nucleated red-Giemsa staining erythrocytes). From experimental evidence, animals (mice) which have suffered chromosome damage some 30 hours following exposure to chemicals will exhibit a significant elevation in polychromatic cells, (found easily in ≤ 24-hr old polychromatic cells).

Protocol:

Specific pathogen free, Swiss CD-1 mice, weighing 20 to 30 g were used. Groups of five males and five females were administered bioallethrin (H3565, batch 79) in sesame oil via the oral route, in two equal doses 24 hours apart as follows: for males, 100, 200, and 400 mg/kg; for females, 75, 150, and 300 mg/kg. The vehicle control was sesame oil administered in two dose groups; one given 0.3 ml and the other 0.6 ml. The highest doses were close to the mouse LD_{50} (= 445 mg/kg in males and 330 mg/kg in females).

The positive control was triethylene melamine (TEM), a known mouse mutagen, which was administered intraperitoneally in two equal doses, 24 hrs apart; total dosage was 0.25 mg/kg. Two dose groups were set up, so that a dose response relationship could be observed, with males and females injected i.p. with 0.125 or 0.250 mg/kg - TEM. Six hours after the second doses, animals were sacrificed and femurs dissected out. Bone marrow smears were prepared (Von Ledebart and Schmid, 1973 method), which were stained in May-Grunwald solution and Giemsa stained. Two thousand polychromatic erythrocytes were examined per animal. Statistical analysis was by the Dunnett test.

Results:

1. Microbial Assays

a. E. coli:

Bioallethrin was not mutagenic in the E. coli inhibition test (at treatment levels of 1250, 2500, and 5000 µg/ml; results were no different from the solvent controls).

positive controls using MNNG were satisfactory; ratios of 2.3, 2.0, and 1.7 for 50, 100, and 200 µg MNNG were obtained for E. coli p3478/WP2 and 1.64, 1.32, and 1.28 for E. coli CM611/WP2.

b. Salmonella Assays:

None of the strains tested without S-9 mix gave a reverse mutation rate elevated over the spontaneous reversion rate. But with microsomal activation, strains TA1535 and TA100 yielded numbers of mutants for which means were in excess of the spontaneous reversion rate. On statistical analysis mean values were at a low order of significance, (89% versus the usually accepted 95%). The results showed d-Trans allethrin not to be mutagenic in the Ames test with strains TA1537, TA1538, and TA98 with and without MA. Salmonella strains TA100 and TA1535 yielded numbers of mutants in excess of control values, only with MA; the mutant frequency was not statistically significant, (but may be meaningful--refer to commentary below).

Core Category - Acceptable.

c. Mouse Micronucleus Test Results:

Observations indicated no deaths in any group; and no adverse effects were noted which could be related to the test chemical. Both males and females of the allethrin treated groups showed no elevation in numbers of polychromatic erythrocytes over the values obtained with vehicle-control groups. In contrast, the positive TEM controls for males and females showed clear cut dose response curves, with results positive at the $p \leq 0.01$ level of statistical significance. Under the circumstances of the assay, d-trans allethrin was not mutagenic.

Core Category - Acceptable.

Reviewed by Pamela Hurley
Section 2 . Tox Branch (TS-769C)
Secondary Reviewer Edwin Budd
Section 2 . Tox Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Acute oral toxicity - rat (81-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER Not given MRID NO 00151460

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): RU-SB-79830/A

SPONSOR: Roussel Uclaf, Romainville. France

TESTING FACILITY: Toxicology Dept., Roussel Uclaf. 102-109, Route de Noisy-le-Sec 93230 Romainville, France

TITLE OF REPORT: Esbiol. Acute Oral Toxicity Study in the Rat

AUTHOR(S): L. Audegond, E Collas and R Glomot

REPORT ISSUED: November 5. 1979

IDENTIFYING VOLUME: Volume 4 of 5, Tab SBA-3

CONCLUSION: LD_{50} for males is 574.5 mg/kg (399.6-742.1 mg/kg) and LD_{50} for females is 412.9 mg/kg (219.4-537.0 mg/kg).

Toxicity Category: II

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d-allethrolone (90%) and d-trans chrysanthemic acid of l-allethrolone (5%)
Description: Not given
Batch #(s), Other #(s): Neuville 7L 1193
Purity: Not given
Source: Not given
Vehicle (if applicable): Polyethyleneglycol 200

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes): Male and female CD1 Sprague Dawley rat
Age: Not given
Weight(s): 100-110 grams
Source(s) IFA CREDO breeding colony, 69210 St. Germain Sur L'Arbresle, France

3. Procedure:

The acute oral toxicity of Esbiol in polyethyleneglycol 200 was determined in male and female rats by testing them with a constant volume (10 ml/kg) by gavage at the following dose levels: 350.0, 507.5, 735.9, 1067.0 and 1547.2 mg/kg. Ten animals/sex were selected for each dose level. The animals were observed frequently for clinical signs of toxicity during the day of dosing and twice daily thereafter for up to 14 days. Bodyweights were measured on the day of dosing, weekly thereafter, and at death. All animals, whether sacrificed at the end of the observation period or sacrificed in moribund condition during the observation period were subjected to a complete gross necropsy. LD_{50}'s and the 95% confidence intervals were calculated by the method of Finney adapted to a PDP8 processor.

B. RESULTS:

The following table summarizes the mortality data:

	Dose Levels (mg/kg)				
	350.0	507.5	735.9	1067.0	1547.2
	Mortality				
Males	1/10	5/10	8/10	8/10	9/10
Females	3/10	8/10	8/10	9/10	10/10

Most of the animals died on the day of dosing. The list of clinical signs included intense grooming behavior, preconvulsions, tremors, hyperexcitability, laboured respiration, epistaxis, clonic convulsions, ptosis, hypotonicity, piloerection and locomotion difficulties. The bodyweight gain of all animals alive at the end of the observation period was normal. In males, a slight loss of bodyweight for all animals that died was observed. In females, a loss of weight between 7-9 grams was observed in the 350.0 and 1067.0 mg/kg groups and a slight loss of bodyweight was observed in the highest dose group. Gross necropsies of these animals revealed the following findings: congestion in the stomach (usually fundus) and areas of hemorrhage in the stomach and other organs. The oral LD_{50}'s were calculated to be 574.5 mg/kg (399.6-742.1 mg/kg) for males and 412.9 mg/kg (219.4-537.0 mg/kg) for females.

C. DISCUSSION:

This study appears to be adequately conducted and reported. Core classification is CORE GUIDELINE.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - rabbit (81-4)

TOX. CHEM. NO.: 25A

MRID NO.: 00151466

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): OU-SB-75.03 22/A

SPONSOR: Not given

TESTING FACILITY: Biological Laboratory, Central Research Laboratory, Japan Mosquito Coil Co . Ltd

TITLE OF REPORT: Irritant Effect of Esbiol and Allet rin on the Eye Mucosa of the Rabbit

AUTHOR(S): Y Sakamoto K Matsumoto and H Ogami

REPORT ISSUED: March 22 1975

IDENTIFYING VOLUME: Vol. 4 of 5 Tab SBA-9

CONCLUSION: Esbiol appears to be a minimal irritant under the conditions of the study, however, the results were written in such a way that they are not useful for comparison purposes with similar tests.

Toxicity Category: N/A

Classification: CORE SUPPLEMENTARY pending submission of scoring method for test design.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (95:5)
Description: Not given
Batch #(s), Other #(s): Not given
Purity: Technical grade (% not given)
Source: Not given
Vehicle (if applicable): Corn oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Japanese White Rabbits (male)
Age: Not given
Weight(s): 2.02-2.51 kg

Source(s): Not given

3. Procedure:

Three rabbits were used per group. One eye received corn oil (diluent). The other eye received the test solution (0.1 ml) and the eyelids were securely held for 10 seconds. The following dose levels were used: undiluted Esbiol and a 50% dilution with corn oil. The conjunctiva, shape of the iris and reflex functions were continuously observed for 1 hour after application and at 2, 5, 24, 48 and 72 hours following application. The eyes were also examined with an ophthalmoscope. No scoring procedure was used, but the effects upon the conjunctiva, iris and cornea were recorded using the following symbols: normal, very slight, slight and moderate.

B. RESULTS:

No effects were observed in the eyes treated with corn oil. Following application of Esbiol, the nictitating reflex repeatedly occurred for approximately 10 minutes and the eye remained closed for 5 hours. Slight hyperemia of the conjunctivae was observed, but recovery occurred by 48 hours. Tearing lasted for 5 hours. Very slight sebum secretion was observed in 1 animal given undiluted Esbiol. This animal recovered by 48 hours. There were no other abnormalities observed. The results indicate that Esbiol has a low irritant effect since abnormalities of the iris or cornea did not occur and the reflex functions were normal.

C. DISCUSSION:

Although the study did use a method to indicate the severity of the effects, these were not scored in any fashion. It would be difficult to compare the results of this study to any other scored studies. Therefore, the study falls into the category of CORE SUPPLEMENTARY until the submitter submits a method for scoring the effects.

Reviewed by Pamela Hurley
Section 2 Tox Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/13/87

81-5 (rat rabbi

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - rats and rabbits (81-5)

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151465

TEST MATERIAL: Esbiol

SYNONYMS: S-bioallethrin

STUDY NUMBER(S): SU-SB-75.07.24/A

SPONSOR: Not given

TESTING FACILITY: Juno Medical Research Facilities, Shinshu University Medical School

TITLE OF REPORT: Esbiol Skin Irritant Tests in Rabbits and Rats

AUTHOR(S): J. Motoyama, T. Yanadaira, A. Sakai, T. Minakami

REPORT ISSUED: July, 1975

IDENTIFYING VOLUME: Volume 4 of 5, Tab SBA-6

CONCLUSION: Esbiol did not appear to be dermally irritating to either rats or rabbits under the conditions of the study. However, this study is CORE SUPPLEMENTARY due to unusual test design.

Toxicity Category: IV

Classification: CORE SUPPLEMENTARY due to inadequate reporting and to unusual test design

A MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of (d,l)-allethrolone (95:5)
Description: Not given
Batch #(s). Other #(s) Not given
Purity: Not given
Source: Esbiol Research Committee
Vehicle (if applicable): Corn oil

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes) Shizuoka Wistar rats and Nagano White rabbits male and female
Age: 5 weeks (rats)
Weight(s) 66-78g (rats) and approximately 3 kg (rabbits)
Source(s): Not given

3. Procedures:

Three groups of 5 male and 5 female rats and 3 groups of 3 male and 3 female rabbits were used for the test. The rats were administered either undiluted Esbiol, a solution diluted by 5 times or a solution diluted by 25 times with corn oil. The rabbits received either undiluted Esbiol, a solution diluted by 10 times or a solution diluted by 100 times. Each of the animals were shaved on the dorsal portion of their bodies. The rats received 0.1 ml/100 g bodyweight of the material and the rabbits received 0.5 ml/100 g bodyweight of the material. The treated areas were covered with plastic film and irritation was determined by the occurrence of erythema, edema or incrustation after a period of 24 and 72 hours. No other details were provided. It was ambiguous as to when the material was removed.

B. RESULTS:

There did not appear to be any dermal irritation. All the values for erythema and edema were zero. In the rat, the material appeared to be dermally toxic because all the animals died after 36 hours and thus the values could not be read. This was not the case for the rabbit. PIS=0.

C. DISCUSSION:

It appears that there may have been a mistake in the amount administered to the rabbits. If one calculates how much material they received from this data, the number is 15 ml ! That is far too much material to pour on the animals. Also, it is unknown as to when the material was removed. If it was never removed, then that may be part of the reason so many rats died prior to termination of the test. No information was submitted as to how much of the body surface area was shaved. It does not appear that this material is dermally irritating, however, the study can only be categorized as CORE SUPPLEMENTARY.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

EDB 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral - Rat (82-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151470

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): SU-SB-75.07.19/A

SPONSOR: Not given

TESTING FACILITY: Shinshu University Medical College, Japan

TITLE OF REPORT: The Results of Subacute and Chronic Toxicity Tests in the Rat (6 month study)

AUTHOR(S): I. Motoyama, T. Yanagidaira, A. [illegible]ai and T. Minakami

REPORT ISSUED: July, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-13

CONCLUSION: No statistically significant toxic effects were noted in any of the treated groups when compared to controls. NOEL: 0.3% in diet (males) and 0.15% in diet (females).

Classification: CORE SUPPLEMENTARY. See discussion.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (95:5)
Description: Not given
Batch #(s), Other #(s): Not given
Purity: 95%
Source: Not given

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): male and female Wistar rats
Age: 4 weeks
Weight(s): Not given
Source(s): Shizuoka Prefecture Experimental Animal Agricultural Associatic-

3. Procedure:

a. Dietary Preparation (if applicable): Details not given

Frequency of preparation: Not given

Storage conditions: Not given

Stability Analyses: Not done

Homogeneity Analyses: Not done

Concentration Analyses: Not done

b. Basis For Selection of Dosage Levels:

Not given

c. Animal Assignment and Dose Levels: Two studies conducted concurrently (a 6-month feeding study and a 90-day study). Same dosage levels used.

Test Group	Dose Administered Percent in diet	Main Study - Either 6 Months or 90 Days male and female
Contr.	0	5 (90 days), 10 (6-month)
1	0.01 (male), 0.005 (female)	5 (90 days), 10 (6-month)
2	0.03 (male), 0.01 (female)	5 (90 days), 10 (6-month)
3	0.1 (male), 0.03 (female)	5 (90 days), 10 (6-month)
4	0.3 (male), 0.15 (female)	5 (90 days), 10 (6-month)

d. Procedures for Studies Other Than Feeding and/or Additions, Changes in Feeding Study: None

e. Clinical Observations and Mortality: Twice daily

f. Body Weight Determinations: Daily, days 1-10; every 10 days thereafter (90-day study), every 20 days thereafter (6-month study)

g. Food and/or Water Consumption: When animals weighed

h. Ophthalmological Examinations (if applicable): Not done

i. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals):
At completion of either 90-day or 6-month study

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*		Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*		Mean corpustular HGB conc. (MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*		
	Platelet count*		
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*	x	Cholesterol*
	Potassium*		Globulins
	Sodium*	x	Glucose*
	Enzymes:		Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
	Creatinine phosphokinase*	x	Protein fraction
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		

3) Urinalysis:

Collection times for urine (including # of animals):
At completion of 6-month study.

The following CHECKED (X) parameters were examined:

X		X	
	Appearance*		Glucose*
	Volume*		Ketones*
	Specific gravity*		Bilirubin*
	pH		Blood*
	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

j. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

No deaths or sacrifices prior to termination of studies.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

All animals.

k. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

None.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

90-day study: 4 controls/sex, 3 mid-dose animals/sex, 2 high dose animals/sex. 6-month study: 7 controls/sex, 5 mid-dose animals/sex, 3 high dose animals/sex.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		Aorta*	xx	Brain* (cerebrum, cerebellum)
	Salivary glands*	xx	Heart*		Periph. nerve*
	Esophagus*	x	Bone marrow*		Spinal cord (3 levels)*
	Stomach*		Lymph nodes*		Pituitary*
	Duodenum*	xx	Spleen*		Eyes (optic n.)*
	Jejunum* (x -intest.)	xx	Thymus*		Glandular
	Ileum*		Urogenital	xx	Adrenals*
	Cecum*	xx	Kidneys*		Lacrimal gland
	Colon*		Urinary bladder*		Mammary gland*
	Rectum*	xx	Testes*		Parathyroids*
xx	Liver*		Epididymides	x	Thyroids*
	Gall bladder*		Prostate		Other
x	Pancreas*		Seminal vesicle		Bone*
	Respiratory	xx	Ovaries		Skeletal muscle*
	Trachea*		Uterus*		Skin
xx	Lung*				All gross lesions and masses

l. Statistical Analyses: Not stated.

B. RESULTS:

1. Dietary Preparation: Not done

2. Clinical Observations and Mortality: No deaths in either study. No clinical signs related to treatment.

3. Body Weight Determinations: A slight inhibition of weight gain in the highest dose group (both male and female, 90-day). In 6-month study, inhibition of weight gain in males of highest dose group and slight

inhibition in second highest group. In females, slight inhibition in weight gain in both highest does levels. Differences not significant (not stated whether or not this applies to all groups).

4. Food and/or Water Consumption: No differences between control and treated groups (according to authors).

5. Ophthalmological Examinations: Not done

6. Hematology: No significant differences found (according to author, not known what statistics used).

7. Clinical Chemistry: In both studies, BUN was somewhat high in male high dose and in female 0.03 and 0.15% dose groups. In the 6-month study, the female 0.01% group was slightly high as well. The authors state that the values were all within normal limits. In the 6-month study, SGPT was somewhat high in the high dose males and females. The differences were not significant, however (according to author).

8. Urinalysis: No differences noted.

9. Gross Pathology: No gross abnormalities observed.

10. Organ Weights: No significant differences between dosed and treated groups in either study.

11. Histopathology:

    a. Nonneoplastic lesions: No changes related to treatment were noted.

    b. Neoplastic lesions: No changes related to treatment were noted.

12. Quality Assurance Measures: Not done.

C. DISCUSSION:

This study is classified as CORE SUPPLEMENTARY. The following list gives some of the reasons:

1. Although some information can be obtained from the studies (a 6-month and a 90-day study) histopathology examinations were conducted on too few animals (at the most, 7/10 control animals of each sex, 5 animals of each sex from the intermediate dose levels and 3 of each sex from the highest dose level).

2. No dietary analyses were conducted.

3. Hematology and clinical chemistry studies were only conducted at termination of the studies. No baseline data was obtained.

4. No ophthalmological examinations were conducted.

5. The following organs that have been suggested for histopathological examinations in the Guidelines were not examined: pituitary, parathyroid (thyroid was examined, so this may have been included), salivary glands, uterus, aorta, esophagus, stomach, urinary bladder, lymph node and peripheral nerve. In addition, it is unknown as to which sections of the intestine were examined.

6. It is unknown as to what statistical analyses were conducted. The data could not be verified.

Reviewed by: Pamela Hurley
Section 2 , Tox Branch (TS-769C)
Secondary Reviewer Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

82-4 (rat mouse)

DATA EVALUATION REPORT

STUDY TYPE: Inhalation - Subacute (1 month) - Rats and Mice

TOX. CHEM. NO.: 25A

ACCESSION NUMBER Not given MRID NO. 00151467

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): OU-SB-75.05 27/A

SPONSOR: Not given

TESTING FACILITY: Central Research Laboratory, Japan Mosquito Coil Co., Ltd.

TITLE OF REPORT: Esbiol Subacute Inhalation Toxicity Tests in the Mouse and Rat

AUTHOR(S): Y. Sakamoto, K. Matsumoto, H. Ogami, M. Yoshimura, N. Sano and T. Shimada

REPORT ISSUED: May 27, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-10

CONCLUSION: This study is classified as CORE SUPPLEMENTARY. The animals were exposed to an aerosol of the substance for periods of 2 hours/day, 6 days/week for one month. No particle size analyses were conducted so that it was unknown as to what particle sizes the animals were being exposed to. Esbiol was dissolved in deotomisol at concentrations of 0.5%, 2.5% and 5% and tested in the animals as an aerosol. The results indicated that clinical signs of toxicity included excitation, tail raising, jumping, salivation and slight trembling in the mouse, and slight salivation and nasal hemorrhaging in the rat in the 2.5% and 5.0% groups. One female mouse in the 2.5% group and 4 female mice in the 5% group died. No significant histopathological changes were noted in these animals when compared to controls. No other signs of toxicity were noted. The clinical signs of toxicity in mice were observed daily during exposure and some continued after completion of exposure, but not during the next day. In rats, the nosebleeds and salivation disappeared after 3 weeks.

83-3 (rat)

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Rats (83-3) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151471

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S) CP-SB-75 02 28/A

SPONSOR: Not given

TESTING FACILITY General Research Laboratory Chugai Pharmaceutical Co . Ltd

TITLE OF REPORT: Esbiol Teratological Tests Results in Rats and Mice

AUTHOR(S): N. Shioda, O Sugiyama Y Takagaki

REPORT ISSUED: February 1975

IDENTIFYING VOLUME Volume 5 of 5 Tab SBA-14

CONCLUSION: Under the conditions of the study it appears that Esbiol is not teratogenic at the dose levels tested. Maternal toxicity NOEL 0.025 ml/kg Fetotox NOEL 0.1 ml/kg

Classification: CORE SUPPLEMENTARY. See discussion

A. MATERIALS AND METHODS

1 Test Compound(s)

Chemical Name: d-trans chrysanthemic acid of d,l, allethrolone (95:5)
Description: Oily liquid with a high specific gravity
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Olive oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Wistar-Imamichi rats
Age: Mature male and female rats
Weight(s): 270g (female rats)
Source(s): Experimental Animal Center of Research Laboratory

3. Procedure:

A preliminary study was conducted with mature male and female rats and with pregnant rats in order to determine the dosages to be used in the main study. Esbiol was diluted with olive oil using two dilution ratios, a 20x dilution and a 40x dilution. All the test groups were dosed by gavage, once per day for 6 days (days 9-14 of the pregnant rats). The male rats were dosed orally with 0.1, 0.2 and 0.4 ml/kg Esbiol (20x dilution) and with 0.1, 0.2, 0.4 and 0.8 ml/kg Esbiol (40x dilution). The female rats were dosed with 0.025, 0.05 and 0.1 ml/kg Esbiol (20x dilution) and with 0.05, 0.1, 0.2 and 0.4 ml/kg Esbiol (40x dilution). The pregnant rats were dosed with 0.2 and with 0.1 ml/kg Esbiol (20x dilution) and with 0.2 ml/kg (40x dilution). Six-day oral LD_{50}'s were estimated from these preliminary test results. Based upon results from the preliminary study, the following dose levels were selected for the main study: 0.025, 0.05 and 0.1 ml/kg Esbiol (40x dilution). Control animals received 4 ml olive oil per kg body weight.

Mature young healthy female rats were selected for the main part of the study. They were confirmed to have undergone at least 2 sexual cycles. The females were placed together with mature male rats of the same strain in the evening. The following morning they were examined for the presence of sperm in the vagina. This day was considered to be day 0 of pregnancy. The following numbers of pregnant animals were tested: 0.2 ml/kg (prelim. study) - 11, 0.1 ml/kg - 22, 0.05 ml/kg - 23, 0.025 ml/kg - 21 and 0ml/kg 21 animals. Esbiol was administered by gavage at the dose levels listed above on days 9-14 of pregnancy. Bodyweights of the dams were determined on the day of mating and on days 3, 6, 9-15, 18 and 21 of pregnancy. They were observed daily for clinical signs of toxicity. On day 21, the dams were sacrificed by cervical dislocation and grossly examined. The following organs weights were measured: liver, spleen, kidneys, ovaries, adrenals, thymus, pituitary, uterus and intestine (stomach to rectum). The viable fetuses were given external examinations, killed by ether anesthesia and given internal gross examinations (no details given). The following observations were recorded: number of implantation sites, embryonic and fetal deaths and viable fetuses; the sex of the fetuses; the viable fetus weights and placenta weights; external abnormalities and skeletal abnormalities. In addition, the death rate, sterility rate (% which did not conceive) and pregnancy maintenance rate (% which did not abort) were recorded for the dams in each dose level.

B. RESULTS:

1. Maternal Toxicity

Death rate, sterility rate and pregnancy maintenance were similar for controls and all treated groups in the main study. At a dose level of 0.2 ml/kg used in the preliminary study, death rate was significantly elevated and pregnancy maintenance rate was significantly depressed (if compared to controls from the main study). Sterility rate was similar to that found in the main study for all groups. Clinical signs of toxicity appeared in almost all the dams at the 0.1 ml/kg dose level. Tremors, salivation, piloerection, blood-like discharge from the eyes and increased

hypersensitivity to sound stimulus were observed in these animals 1 to 2 hours following dosing. The tremors disappeared 2-4 hours following the initial dose, but became more marked as the number of times of dosing increased. One animal from the 0.1 ml/kg group died on day 6 and one animal from the 0.05 ml/kg group died on day 2. Hypertrophy of the liver, roughness of the liver parenchyma and congestion of the brain and heart were noted in these animals upon autopsy. The results of the preliminary test with the pregnant rats dosed at the 0.2 ml/kg level were mixed in with the results from the main study. Bodyweight gain was not inhibited in any of the treated groups (except in the 0.2 ml/kg group when included with the main study results). No significant differences in the organ weights of any of the treated groups were noted (except in the 0.2 ml/kg group which indicated atrophy of the thymus).

In all of the dosed groups used in the main study, there were no significant differences in the treated animals versus the controls with respect to number of implantations, number of viable fetuses, frequency of embryonic (fetal) death, lethality with respect to sex or placental weight. There was a tendency towards inhibition of viable fetal body weight with increasing dose, however, the differences were not statistically significant with respect to the control group. There were no external abnormalities in any of the groups in the main study. In the preliminary study, one dam in the 0.2 ml/kg group had 1 fetus with cleft palate and 7 with a reduced number of digits. The report only contained 1 summary table on skeletal abnormalities. The table listed total number of fetuses with abnormalities/dose level and the number of fetuses with either cervical, thoracic or lumbar abnormalities/dose level. The abnormalities included incomplete ossification of certain vertebrae, fusions of certain vertebrae, asymmetry and transformation of lumbar into thoracic vertebrae. One variation which appeared to increase with increasing dose was transformation of lumbar vertebrae to thoracic vertebrae: (45/230 (control), 48/227 (0.025), 66/222 (0.05), and 104/246 (0.1 ml/kg)). The authors stated, "In consideration of the frequency and severity of each type of abnormality, and the fact that compounded skeletal abnormalities, with the exception of compounded abnormalities of a variant formation, only occurred in 1 fetus (0.2 ml/kg group, preliminary study: fusion of the right 1st and 2nd thoracic vertebral arch + fusion of the 11th and 12th ribs), Esbiol does not appear to have a particularly great great effect on the process of skeletal formation in the fetus." In examining the data, it appears that the authors may be correct in their conclusions, however, one table is insufficient in order to verify their statement.

C. DISCUSSION:

This study had a number of problems. The following is a list of questions and/or deficiencies:

1. Results from the preliminary study were mixed in the the results from the main study. This is not good science and should not be done. Results from two separate studies conducted at two different times should not be compared. There are too many variables involved.

2. The pregnant animals were only dosed from day 9 to 14. The Guidelines

state that they should be dosed from days 6-15. Dosing from days 9-14 may cause some important data to be missed.

3. There were no details as to how the soft tissue examinations were conducted. There were no tables on soft tissue examinations either. Someone reviewing the study would not know what was examined and what was not.

4. There was no indication that the investigators examined the heads. This is important. An observed cleft palate in the gross external examination should have been verified by a skeletal abnormality. It was not mentioned.

5. There were no details in the skeletal abnormality tables. One cannot tell which fetuses were examined for what abnormality or whether or not one fetus had multiple abnormalities. The table is insufficient.

6. Corpora lutea were not counted. This is necessary in order to tell whether or not there were any pre-implantation losses (although it is not likely that this would have happened in this case because the dosing was started so late).

This study is classified as CORE SUPPLEMENTARY since some information can be obtained from it, although it is not adequate as a teratology study.

Reviewed by Pamela Hurley
Section 2 . Tox Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

4/23/87

83-3 (mouse)

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Mice (83-3) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151471

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): CP-SB-75.02.28/A

SPONSOR: Not given

TESTING FACILITY: General Research Laboratory, Chugai Pharmaceutical Co., Ltd.

TITLE OF REPORT: Esbiol Teratological Tests Results in Rats and Mice

AUTHOR(S): N. Shioda, O. Sugiyama, Y. Takagaki

REPORT ISSUED: February, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-14

CONCLUSION: Under the conditions of the study, it appears that Esbiol is not teratogenic at the dose levels tested. Maternal toxicity NOEL could not be established. Fetotox. NOEL 0.1 ml/kg (HDT in main study).

Classification: CORE SUPPLEMENTARY. See discussion.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l, allethrolone (95:5)
Description: Oily liquid with a high specific gravity
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Olive oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Tvcs mice
Age: Mature males and 80-100 day old females
Weight(s): 25-30 grams (females)
Source(s): Experimental Animal Center of Research Laboratory

3. Procedure:

A preliminary study was conducted with pregnant mice in order to determine the dosages to be used in the main study. Esbiol was diluted with olive oil using 3 dilution ratios, a 10x dilution, a 50x dilution and a 100x dilution. The animals were dosed by gavage, once per day for 6 days (days 7-12 of the pregnant mice). Each dilution ratio was tested with either one or two doses of undiluted Esbiol : 1.0 and 0.5 ml/kg Esbiol (10x dilution), 0.1 ml/kg Esbiol (50x dilution) and 0.2 and 0.1 ml/kg Esbiol (100x dilution).

Based upon results from the preliminary study, the following dose levels were selected for the main study: 0.05 and 0.1 ml/kg Esbiol (100x dilution).

Mature young healthy female mice were selected for the main part of the study. They were confirmed to have undergone at least 1 sexual cycle. The following numbers of females were used: 5(0.2 ml/kg), 29(0.1 ml/kg), 29(0.05 ml/kg) and 23 (controls). The females were placed together with mature male mice of the same strain in the evening. The following morning they were examined for the presence of a vaginal plug. This day was considered to be day 0 of pregnancy. Esbiol was administered by gavage at the dose levels listed above on days 7-12 of pregnancy. Bodyweights of the dams were determined on the day of mating and on days 3, 6-13, 15 and 18 of pregnancy. They were observed daily for clinical signs of toxicity. On day 18, the dams were sacrificed by cervical dislocation. The viable fetuses were given external examinations, killed by ether anesthesia and given internal gross examinations (no details given). The following observations were recorded: number of implantation sites, embryonic and fetal deaths and viable fetuses; the sex of the fetuses; the viable fetus weights and placenta weights; external abnormalities and skeletal abnormalities. In addition, the death rate, sterility rate (animals for which implantation sites were not observed) and abortion rate were recorded for the dams in each dose level.

B. RESULTS:

1. Maternal Toxicity:

The results from the preliminary study were combined with the results from the main study. No deaths occurred in the control and 0.05 ml/kg groups (0/23 and 0/29, respectively). Two of 29 animals died in the 0.1 ml/kg group and 2/5 animals died in the 0.2 ml/kg group (from the preliminary study). Clinical signs of toxicity (tremors) occurred in the two top dose levels. There was a tendency towards increased abortion and sterility rate in all the treated groups. The authors state that they were not statistically significant when compared to controls, however, they appear to be biologically significant. There were no differences in body weight gains between the groups. Very little data was presented to support these statements.

2. Embryo/Fetotoxicity:

There were no differences between the control and treated groups with respect to average number of implantations, the incidence of embryonic/fetal deaths, the average number of viable vetuses, fetal body weight and sex ratios, and the average weight of the placenta. One fetus with cleft palate and hydrocephalus and 1 with cleft palate alone were observed out of 229 fetuses in the 0.1 ml/kg group. In the control group, 1 fetus with an abdominal hernia and 1 fetus with hydrocephalus were noted out of 207 fetuses. No skeletal malformations were noted that appeared to be related to treatment with Esbiol. The types of skeletal abnormalities observed were insufficient ossification of occipital bone (1/207 controls and 1/229 high dose group), separation of left and/or right 1st vertebral arch (3 controls, 6/196 mid-dose, probably 3 high dose group, one number omitted), either left and right asymmetry of the sternum (1 each control and high dose) and incomplete ossification of the 5th sternum (2 mid-dose).

C. DISCUSSION:

This study had a number of problems. The following is a list of questions and/or deficiencies:

1. Results from the preliminary study were mixed in the the results from the main study. This is not good science and should not be done. Results from two separate studies conducted at two different times should not be compared. There are too many variables involved.

2. The pregnant animals were only dosed from day 7 to 12. The Guidelines state that they should be dosed from days 6-15. Dosing from days 7-12 may cause some important data to be missed.

3. There were no details as to how the soft tissue examinations were conducted. There were no tables on soft tissue examinations either. Someone reviewing the study would not know what was examined and what was not.

4. There were no details in the skeletal abnormality tables. One cannot tell which fetuses were examined for what abnormality or whether or not one fetus had multiple abnormalities. The table is insufficient.

5. Corpora lutea were not counted. This is necessary in order to tell whether or not there were any pre-implantation losses (although it is not likely that this would have happened in this case because the dosing was started so late).

6. In general, too little information was supplied on the procedures used for the study and too little data were supplied in reporting the results. Therefore, the results could not be verified by the scanty information supplied.

This study is classified as CORE SUPPLEMENTARY since some information can be obtained from it, although it is not adequate as a teratology study.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Acute oral toxicity - rat (81-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO: PHES0001

TEST MATERIAL: Esbiothrin

SYNONYMS: None

STUDY NUMBER(S): RU-EBT-79828/A

SPONSOR: Roussel Uclaf, Romainville, France

TESTING FACILITY: Toxicology Dept., Roussel Uclaf. 102-109, Route de Noisy-le-Sec 93230 Romainville, France

TITLE OF REPORT: Esbiothrin. Acute Oral Toxicity Study in the Rat

AUTHOR(S): L. Audegond, E. Collas and R. Glomot

REPORT ISSUED: November 5, 1979

IDENTIFYING VOLUME: Volume 3 of 5, Tab EBT-1

CONCLUSION: Oral LD_{50} for males in PEG 200 is 432.3 mg/kg (270.5-728.3 mg/kg) and LD_{50} for females is 378.0 mg/kg (219.3-555.6 mg/kg).

Toxicity Category: II

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d-allethrolone (72%) and d-trans chrysanthemic acid of l-allethrolone (21%)
Description: Not given
Batch #(s), Other #(s): 9 L 1069
Purity: Not given
Source: Not given (assumed Roussel Uclaf)
Vehicle (if applicable): Polyethyleneglycol 200

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female CD1 Sprague Dawley rat
Age: Not given
Weight(s): 100-110 grams
Source(s): IFFA CREDO breeding colony, 69210 St. Germain Sur L'Arbresle, France

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE October 4, 1979

SUBJECT: EPA File No. 1021-1060, D-Trans Allethrin: teratogenic evaluation. CASWELL #25A

FROM John Doherty 10/17/79 Budd 10/17/79
Toxicology Branch/HED (TS-769)

TO Franklin Gee
Product Manager#17/RD (TS-767)

Conclusion:

The teratology study in rats has been reviewed and it is concluded that d-trans allethrin is not a teratogen in rats at doses as high as 195 mg/kg/ day (highest level tested).

However, at all test levels there was a significantly increased number of fetuses with rudimentary 14th ribs. This is considered a possible fetotoxic effect and no NOEL is established for this effect.

Toxicology Branch requests information on the detailed history of this lesion (rudimentary 14th ribs) in the strain of rats used for this study to determine if this effect is allethrin dependent.

Teratologic Evaluation of D-Trans Allethrin in Sprague Dawley Rats.

Food and Drug Research Laboratories, April 20, 1979, Lab. No. 6059. (In EPA accession No. 238638)

6 groups of female rats (28-34 per group) were used in this experiment. The doses of d-trans allethrin (92.5%) used were 50, 125, 195 and 300 mg/kg/day. The group receiving 300 mg/kg/day was terminated after the first few doses because this dose was lethal to the dams. Vehicle control and positive control (aspirin, 250 mg/kg/day) groups were also run.

The dams were impregnated and treated by gavage on days 6-15 of gestation. The rats were sacrificed on day 20 and the uterine contents and the pups subjected to thorough examination.

Results (for controls, 50, 125 and 195 mg/kg/day d-trans allethrin)

1) The dams gained weight normally and were reported as not having changes in general appearance and behavior. There were 6 deaths in the high dose group (195 mg/kg).

2) There were no differences in pregnancy, implantation, numbers of dead or live fetuses, or number of resorption sites/dam reported.

3) There were no reported soft tissue anomalies in fetuses from d-trans allethrin treated dams.

4) The single statistically significant abnormality reported for skeletal development was a significant increase in the % of litters with rudimentary 14th ribs at all doses of d-trans allethrin tested.

		D-Trans Allethrin		
Vehicle Control	Aspirin	50 mg/kg	125 mg/kg	195 mg/kg
10/5	58/17*	18/10*	38/19*	34/15*

upper = number of fetuses affected.
lower = number of litters affected.
* significantly different from control.

There was also an increased incidence of incomplete ossification of the vertebrae at all levels of d-trans allethrin, but this was not statistically significant.

This is a CORE-GUIDELINES study.

TOX/HED:th:RD Initial EBUDD:9-21-79 Rewrite:Budd:sb:10/5/79

iewed by: Pamela Hurley
tion 2 , Tox. Branch (TS-769C)
ondary Reviewer: Edwin Budd
tion 2 , Tox. Branch (TS-769C)

4/23/87

84-2
Chinese Hamster

DATA EVALUATION REPORT

STUDY TYPE: Chromosomal Aberration - CHL cells (84-2)

TOX. CHEM. NO.: 25 or 25A

ACCESSION NUMBER: Not given

MRID NO.: 00141594

TEST MATERIAL: Allethrin

SYNONYMS: Not sure which isomer this is

REPORT NUMBER: Mutation Research 66: 277-290. 1979

TESTING FACILITY: National Inst. of Hygienic Science, Tokyo, Japan

TITLE OF REPORT: Chromosomal Aberration Tests on 29 Chemicals Combined with S-9 Mix In Vitro

AUTHOR(S): A. Matsuoka, M. Hayashi and M. Ishidate

REPORT ISSUED: Sept. 15, 1978

CONCLUSION: This study was reviewed earlier (see memo from M. Sochard to A. Heyward (8/7/85). The present reviewer agrees with the conclusions of the previous reviewer (see additional comments below).

Classification: UNACCEPTABLE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: Allethrin (isomer ratios not given).
Description: Not given
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Either ethanol, DMSO or saline

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes): Chinese hamster lung cells

Additional Comments

There are other problems with this study that render it impossible to use as a chromosomal aberration study for bioallethrin. First of all, the authors stated that allethrin was tested. Technical Allethrin is different from technical Bioallethrin. No distinction was made. On this basis alone, the study is unusable without further identification of the test chemical. No purities were given either. The vehicle used was unclear. It was one of 3 choices mentioned in the script of the report. The study should be repeated, especially since the results were positive.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

AUG 7 1985 000596

MEMORANDUM

SUBJECT: 1021-1217. d-trans allethrin (Bioallethrin)
Mutagenicity Assays

Tox. Chem. No. 25A
(Related are Nos. 670, 613, 77A)

FROM: M. R. Sochard, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: A. Heyward, PM Team #17
Registration Division (TS-767)

THRU: E. R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant

McLaughlin Gorman King Company
8810 Tenth Avenue N.
Minneapolis, MN 55427

Matsuoka, A.; Hayashi, M.; Ishidate, M. Jr. (1979) Chromosomal Aberration Tests on 29 Chemicals Combined with S-9 In Vitro. Mutation Research, 66:277-290. Submitted as part of Accession No. 252029.

Protocol:

A group of 29 chemicals which included allethrin, was assayed in CHL cells (chinese hamster lung cells) following treatment with S-9 mix. Test chemicals were assayed at three different doses of each, with cell cultures and chemicals incubated with shaking at 37 °C for 3 hours. Cells were then cultured in 6-cm culture dishes for 24 hours longer. Cells were colcemid treated, prepared for microscopic examination on microscope slides, and stained with Giemsa stain. One hundred well spread metaphases were counted. Chromosome aberrations were classified as follows: chromatid gaps, chromatic breaks, chromatid or chromosomal exchanges, ring formation and fragmentation, or pulverization of chromosomes. Polyploidy was also sought and recorded. Results were recorded as negative if less than 4.9 percent aberrations were seen including at high doses tested even if at sublethal concentrations.

A (+) was assigned to aberrations between 5.0 and 9.9 percent (suspicious). A positive was assigned if aberrations were at 10 to 19.7 percent (+); 20 to 49.9 percent (++) and more than 50 percent was assigned (+++). Controls included untreated and

Results:

In the above syster, with S-9 mix, allethrin was a strong positive (+++); at the 77 percent level, with chromatic gaps, chromatid breaks, chromatic or chromosome exchanges, fragmentation pulverization of chromosomes and ring formation seen at a dose-level of 0.0019 mg/ml (no other dose level results given). The conclusion was that under the circumstances reported, allethrin is mutagenic with S-9 mix. Since results are reported only for one dose level of allethrin, the study is considered unacceptable for regulatory purposes.

Core Category - Not acceptable.

ewed by: Pamela Hurley
ion 2 , Tox. Branch (TS-769C)
ndary Reviewer: Edwin Budd
ion 2 , Tox. Branch (TS-769C)

Bydd 4/23/87

84-2
S. typh.
E. coli
Mouse

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity (84-2) - Growth Inhibition in E. Coli, Reverse Mutation in S. typhimurium and Mouse Micronucleus

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: 252029

MRID NO.: 00133570

TEST MATERIAL: Bioallethrin

SYNONYMS: d-trans Allethrin

REPORT NUMBER: RU-BA-79.27.12/A

SPONSOR: Roussel Uclaf, Romainville, France

TESTING FACILITY: Centre de Recherches, Roussel Uclaf, Romainville, France

TITLE OF REPORT: Detection of a Mutagenic Potency of Bioallethrin

AUTHOR(S): M. Peyre, J.F. Chantot, L. Penasse, B. Vannier and R. Glomot

REPORT ISSUED: December 27, 1979

IDENTIFYING VOLUME: Volume 2 of 5, Tab BA-9

CONCLUSION: These 3 studies were reviewed previously (see memo from M. Sochard to A. Heyward (attached)). This reviewer agrees with the conclusions reached for two of the studies, but disagrees with the conclusions reached on the mouse micronucleus study. The studies indicate that under the specified conditions for microbial assays, The E. Coli DNA damage and repair tests and the Salmonella Ames tests for forward mutation were negative for Bioallethrin. However, Salmonella strains TA100 and TA1535 gave weak but positive results with metabolic activation. The mouse micronucleus assay was negative under the conditions of the bioassay.

Classification: The Ames study and the DNA damage and repair test were ACCEPTABLE but the mouse micronucleus test was UNACCEPTABLE unless additional data can be submitted (see comments on next page).

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (46.5:46.5)
Description: Not given (solid?)
Batch #(s), Other #(s): BL1461 (Ames), H 3565 batch 79 (mouse micronucleus)
E. coli assay - not given

Purity: Not given
Source: Not given

Vehicle (if applicable): DMSO (Ames and E. coli); sesame oil (micronucleus)

Positive Control(s) (if applicable): N-methyl N'-nitro-N-nitrosoguanidine (MNNG) (E. coli); 2-Aminoanthracene, MNNG, 9-Aminoacridine, 2-nitrofluorene (Ames); Triethylene melamine (TEM) (mouse micronucleus).

Comments:

This reviewer disagrees with the conclusion of the previous reviewer on the mouse micronucleus assay. There are three problems with the assay. First of all, TEM was administered i.p.. As a positive control, it should have been administered orally, as bioallethrin was administered. Secondly, there is some confusion concerning the dosage levels administered. Since no toxicity was observed, were these animals the same strain as those for which the LD_{50} was reported? It should have been stated as such. Thirdly, there was no evidence of toxicity, either clinical signs with the animals or cytotoxicity. The study cannot be properly evaluated without submission of additional data (if available). The data needed are:

1. Data concerning the ratio of PCE's to normochromatic erythrocytes, or some other indication of possible toxicity.

2. The strain of mouse in the quoted LD_{50} study.

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

AUG 7 1985 004596

MEMORANDUM

SUBJECT: 1021-1217. d-trans allethrin (Bioallethrin)
Mutagenicity Assays

Tox. Chem. No. 25A
(Related are Nos. 670, 613, 77A)

FROM: M. R. Sochard, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: A. Heyward, PM Team #17
Registration Division (TS-767)

THRU: E. R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant

McLaughlin Gorman King Company
8810 Tenth Avenue N.
Minneapolis, MN 55427

Peyre, M. et al. Dated November 28, 1979, Unpublished. Detection of a Mutagenic Potency of Bioallethrin. Roussel Uclaf. (36 pages, Microbial Assays as Well as Micronucleus Test in Mice).

The Peyre et al. studies indicate that under the specified conditions for the microbial assays, the E. coli DNA damage and repair tests and the Salmonella Ames tests for forward mutations were negative for bioallethrin. However, Salmonella strains TA100 and TA1535 gave weak but positive results when metabolic activation (S-9 mix) was included in the assay. Both microbial assays were Core Category - Acceptable.

The Peyre et al. mouse micronucleus assay showed bioallethrin was ...tive for micronuclei induction in bone marrow of mice ...inistered the chemical at levels up to a lethal dose.

Core Category: Acceptable.

Detection of a Mutagenic Potency of BioAllethrin. 1. Microbial Assays. 2. Micronucleus test in Mouse. Peyre, M.; Chantot, J.F.; Penasse, L.; Vannier B.; Glomot, R. Romainville, December 27, 1979. 36 pages. Accession No. 252029.

Protocol:

A. Microbial Assays

a. E. coli Assays, Using Bioallethrin (Batch no. 8L1461)

Growth inhibition by allethrin was compared using wild type E. coli and three mutant strains derived from the wild type which are deficient in certain repair mechanisms. E. coli strains, auxotrophic for tryptophan (trp^-) with varying proficiency in DNA repair mechanisms were compared as matched pairs for inhibition tests with test chemical. Thus, strain WP_2 derived from the wild type and having the genome trp^-, $uvra^+$, exr^+ is unable to grow without tryptophan; and proficient at excision DNA repair and is free of error-prone rec-dependent DNA repair. Its counterpart is strain CM611, trp^-, $uvra^-$ and $exrA^-$, deficient in excision-repair of DNA and has the defect error-prone, rec-dependent DNA repair. E. coli strain WP_2, thy^- and pol A^+ is unable to grow without thymine and tryptophan, but is proficient for DNA polymerase I.

Its counterpart is E. coli strain p3478 which is auxotrophic for trp^- and thy^- and in addition, is deficient in DNA polymerase I. The assay was done as follows: Dilutions of allethrin at 1250, 2500, and 5000 µg/ml were placed in wells cut into agar plates which were inoculated with bacteria so as to obtain confluent growth. As the chemical diffused through the agar it contacted the bacteria, and growth inhibition was measured, following incubation of the cultures for 18 hours at 37 °C. The positive control, N-methyl N'-nitro-N-nitrosoguanidine (MNNG) should give growth inhibition ratios between the paired E. coli greater than 1.0. The control antibiotic (chloramphenicol) should provide paired ratios of 1.0. A solvent control (DMSO) was included.

b. Salmonella Assays

Bioallethrin was tested with and without MA (metabolic activation with S-9 mix) in concentrations ranging [illegible] 2 to 5,000 µg per plate. Mutant bacteria were genetically constructed so that each strain had a different genetic defect within a genome which can be reverted to the wild type by a single mutation. A chemical-induced mutation (reversion) in any or all strains indicates a specific genetic event. (Dilutions of Bioallethrin in DMSO (solvent) were easily precipitated in culture medium at concentrations of 200 µg per plate and above.) For the test, agar plates with minimal medium were overlaid with soft agar containing admixtures of

selected diluted test chemical, selected Salmonella bacteria, with or without S-9 mix; separate plates were prepared to provide positive, negative, or vehicle (DMSO) controls. Four agar plates were prepared for each dilution per assay and data obtained were analyzed using statistical methods. Salmonella strains used were TA1535, TA100, TA1537, TA1538, and TA98.

b. Micronucleus Assay

This test is based on observations that chromosome damage may be assessed from the number of polychromatic erythrocytes in excess of normal in bone marrow of animals exposed to test chemicals. Polychromatic cells (stained blue with Giemsa stain) are normally few in number, found in marrow, and represent those erythrocytes which have not yet extruded their nuclei (normally, such cells extrude their nuclei and are recognized as non-nucleated red-Giemsa staining erythrocytes). From experimental evidence, animals (mice) which have suffered chromosome damage some 30 hours following exposure to chemicals will exhibit a significant elevation in polychromatic cells, (found easily in ≤ 24-hr old polychromatic cells).

Protocol:

Specific pathogen free, Swiss CD-1 mice, weighing 20 to 30 g were used. Groups of five males and five females were administered bioallethrin (H3565, batch 79) in sesame oil via the oral route, in two equal doses 24 hours apart as follows: for males, 100, 200, and 400 mg/kg; for females, 75, 150, and 300 mg/kg. The vehicle control was sesame oil administered in two dose groups; one given 0.3 ml and the other 0.6 ml. The highest doses were close to the mouse LD_{50} (= 445 mg/kg in males and 330 mg/kg in females).

The positive control was triethylene melamine (TEM), a known mouse mutagen, which was administered intraperitoneally in two equal doses, 24 hrs apart; total dosage was 0.25 mg/kg. Two dose groups were set up, so that a dose response relationship could be observed, with males and females injected i.p. with 0.125 or 0.250 mg/kg - TEM. Six hours after the second doses, animals were sacrificed and femurs dissected out. Bone marrow smears were prepared (Von Ledebert and Schmid, 1973 method), which were stained in May-Grunwald solution and Giemsa stained. Two thousand polychromatic erythrocytes were examined per animal. Statistical analysis was by the Dunnett test.

Results:

1. Microbial Assays

a. E. coli:

Bioallethrin was not mutagenic in the E. coli inhibition test (at treatment levels of 1250, 2500, and 5000 µg/ml; results were no different from the solvent controls).

positive controls using MNNG were satisfactory: ratios of 2.3, 2.0, and 1.7 for 50, 100, and 200 µg MNNG were obtained for E. coli p3478/W3110 and 1.64, 1.32, and 1.28 for E. coli CM611/WP2.

b. Salmonella Assays:

None of the strains tested without S-9 mix gave a reverse mutation rate elevated over the spontaneous reversion rate. But with microsomal activation, strains TA1535 and TA100 yielded numbers of mutants for which means were in excess of the spontaneous reversion rate. On statistical analysis mean values were at a low order of significance, (89% versus the usually accepted 95%). The results showed d-Trans allethrin not to be mutagenic in the Ames test with strains TA1537, TA1538, and TA98 with and without MA. Salmonella strains TA100 and TA1535 yielded numbers of mutants in excess of control values, only with MA; the mutant frequency was not statistically significant, (but may be meaningful--refer to commentary below).

Core Category - Acceptable.

c. Mouse Micronucleus Test Results:

Observations indicated no deaths in any group; and no adverse effects were noted which could be related to the test chemical. Both males and females of the allethrin treated groups showed no elevation in numbers of polychromatic erythrocytes over the values obtained with vehicle-control groups. In contrast, the positive TEM controls for males and females showed clear cut dose response curves, with results positive at the $p \leq 0.01$ level of statistical significance. Under the circumstances of the assay, d-trans allethrin was not mutagenic.

Core Category - Acceptable.

Reviewed by Pamela Hurley
Section 2 . Tox Branch (TS-769C)
Secondary Reviewer Edwin Budd
Section 2 . Tox Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Acute oral toxicity - rat (81-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER Not given MRID NO 00151460

TEST MATERIAL: Esbiol

SYNONYMS: d-trans allethrin

STUDY NUMBER(S): RU-SB-79830/A

SPONSOR: Roussel Uclaf, Romainville. France

TESTING FACILITY: Toxicology Dept., Roussel Uclaf. 102-109, Route de Noisy-le-Sec 93230 Romainville, France

TITLE OF REPORT: Esbiol. Acute Oral Toxicity Study in the Rat

AUTHOR(S): L. Audegond, E Collas and R Glomot

REPORT ISSUED: November 5. 1979

IDENTIFYING VOLUME: Volume 4 of 5, Tab SBA-3

CONCLUSION: LD_{50} for males is 574.5 mg/kg (399.6-742.1 mg/kg) and LD_{50} for females is 412.9 mg/kg (219.4-537.0 mg/kg).

Toxicity Category: II

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d-allethrolone (90%) and d-trans chrysanthemic acid of l-allethrolone (5%)
Description: Not given
Batch #(s), Other #(s): Neuville 7L 1193
Purity: Not given
Source: Not given
Vehicle (if applicable): Polyethyleneglycol 200

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes): Male and female CD1 Sprague Dawley rat
Age: Not given
Weight(s): 100-110 grams
Source(s) IFA CREDO breeding colony, 69210 St. Germain Sur L'Arbresle, France

3. Procedure:

The acute oral toxicity of Esbiol in polyethyleneglycol 200 was determined in male and female rats by testing them with a constant volume (10 ml/kg) by gavage at the following dose levels: 350.0, 507.5, 735.9, 1067.0 and 1547.2 mg/kg. Ten animals/sex were selected for each dose level. The animals were observed frequently for clinical signs of toxicity during the day of dosing and twice daily thereafter for up to 14 days. Bodyweights were measured on the day of dosing, weekly thereafter, and at death. All animals, whether sacrificed at the end of the observation period or sacrificed in moribund condition during the observation period were subjected to a complete gross necropsy. LD_{50}'s and the 95% confidence intervals were calculated by the method of Finney adapted to a PDP8 processor.

B. RESULTS:

The following table summarizes the mortality data:

	Dose Levels (mg/kg)				
	350.0	507.5	735.9	1067.0	1547.2
	Mortality				
Males	1/10	5/10	8/10	8/10	9/10
Females	3/10	8/10	8/10	9/10	10/10

Most of the animals died on the day of dosing. The list of clinical signs included intense grooming behavior, preconvulsions, tremors, hyperexcitability, laboured respiration, epistaxis, clonic convulsions, ptosis, hypotonicity, piloerection and locomotion difficulties. The bodyweight gain of all animals alive at the end of the observation period was normal. In males, a slight loss of bodyweight for all animals that died was observed. In females, a loss of weight between 7-9 grams was observed in the 350.0 and 1067.0 mg/kg groups and a slight loss of bodyweight was observed in the highest dose group. Gross necropsies of these animals revealed the following findings: congestion in the stomach (usually fundus) and areas of hemorrhage in the stomach and other organs. The oral LD_{50}'s were calculated to be 574.5 mg/kg (399.6-742.1 mg/kg) for males and 412.9 mg/kg (219.4-537.0 mg/kg) for females.

C. DISCUSSION:

This study appears to be adequately conducted and reported. Core classification is CORE GUIDELINE.

Reviewed by: Pamela Hurley
Section 2 . Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 . Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - rabbit (81-4)

TOX. CHEM. NO.: 25A

MRID NO.: 00151466

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): OU-SB-75.03 22/A

SPONSOR: Not given

TESTING FACILITY: Biological Laboratory, Central Research Laboratory, Japan Mosquito Coil Co . Ltd

TITLE OF REPORT: Irritant Effect of Esbiol and Allethrin on the Eye Mucosa of the Rabbit

AUTHOR(S): Y Sakamoto K Matsumoto and H Ogami

REPORT ISSUED: March 22 1975

IDENTIFYING VOLUME: Vol. 4 of 5 Tab SBA-9

CONCLUSION: Esbiol appears to be a minimal irritant under the conditions of the study, however, the results were written in such a way that they are not useful for comparison purposes with similar tests.

Toxicity Category: N/A

Classification: CORE SUPPLEMENTARY pending submission of scoring method for test design.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (95:5)
Description: Not given
Batch #(s), Other #(s): Not given
Purity: Technical grade (% not given)
Source: Not given
Vehicle (if applicable): Corn oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Japanese White Rabbits (male)
Age: Not given
Weight(s): 2.02-2.51 kg

Source(s): Not given

3. Procedure:

Three rabbits were used per group. One eye received corn oil (diluent). The other eye received the test solution (0.1 ml) and the eyelids were securely held for 10 seconds. The following dose levels were used: undiluted Esbiol and a 50% dilution with corn oil. The conjunctiva, shape of the iris and reflex functions were continuously observed for 1 hour after application and at 2, 5, 24, 48 and 72 hours following application. The eyes were also examined with an ophthalmoscope. No scoring procedure was used, but the effects upon the conjunctiva, iris and cornea were recorded using the following symbols: normal, very slight, slight and moderate.

B. RESULTS:

No effects were observed in the eyes treated with corn oil. Following application of Esbiol, the nictitating reflex repeatedly occurred for approximately 10 minutes and the eye remained closed for 5 hours. Slight hyperemia of the conjunctivae was observed, but recovery occurred by 48 hours. Tearing lasted for 5 hours. Very slight sebum secretion was observed in 1 animal given undiluted Esbiol. This animal recovered by 48 hours. There were no other abnormalities observed. The results indicate that Esbiol has a low irritant effect since abnormalities of the iris or cornea did not occur and the reflex functions were normal.

C. DISCUSSION:

Although the study did use a method to indicate the severity of the effects, these were not scored in any fashion. It would be difficult to compare the results of this study to any other scored studies. Therefore, the study falls into the category of CORE SUPPLEMENTARY until the submitter submits a method for scoring the effects.

Reviewed by Pamela Hurley
Section 2 Tox Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/13/87

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - rats and rabbits (81-5)

TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151465

TEST MATERIAL: Esbiol

SYNONYMS: S-bioallethrin

STUDY NUMBER(S): SU-SB-75.07.24/A

SPONSOR: Not given

TESTING FACILITY: Juno Medical Research Facilities, Shinshu University Medical School

TITLE OF REPORT: Esbiol Skin Irritant Tests in Rabbits and Rats

AUTHOR(S): J. Motoyama, T. Yanadaira, A. Sakai, T. Minakami

REPORT ISSUED: July, 1975

IDENTIFYING VOLUME: Volume 4 of 5, Tab SBA-6

CONCLUSION: Esbiol did not appear to be dermally irritating to either rats or rabbits under the conditions of the study. However, this study is CORE SUPPLEMENTARY due to unusual test design.

Toxicity Category: IV

Classification: CORE SUPPLEMENTARY due to inadequate reporting and to unusual test design

A MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of (d,l)-allethrolone (95:5)
Description: Not given
Batch #(s). Other #(s) Not given
Purity: Not given
Source: Esbiol Research Committee
Vehicle (if applicable): Corn oil

2. Test Animals and/or Other Test System (if applicable)

Species and Strain (sexes) Shizuoka Wistar rats and Nagano White rabbits male and female
Age: 5 weeks (rats)
Weight(s) 66-79g (rats) and approximately 3 kg (rabbits)
Source(s): Not given

3. Procedures:

Three groups of 5 male and 5 female rats and 3 groups of 3 male and 3 female rabbits were used for the test. The rats were administered either undiluted Esbiol, a solution diluted by 5 times or a solution diluted by 25 times with corn oil. The rabbits received either undiluted Esbiol, a solution diluted by 10 times or a solution diluted by 100 times. Each of the animals were shaved on the dorsal portion of their bodies. The rats received 0.1 ml/100 g bodyweight of the material and the rabbits received 0.5 ml/100 g bodyweight of the material. The treated areas were covered with plastic film and irritation was determined by the occurrence of erythema, edema or incrustation after a period of 24 and 72 hours. No other details were provided. It was ambiguous as to when the material was removed.

B. RESULTS:

There did not appear to be any dermal irritation. All the values for erythema and edema were zero. In the rat, the material appeared to be dermally toxic because all the animals died after 36 hours and thus the values could not be read. This was not the case for the rabbit. PIS=0.

C. DISCUSSION:

It appears that there may have been a mistake in the amount administered to the rabbits. If one calculates how much material they received from this data, the number is 15 ml ! That is far too much material to pour on the animals. Also, it is unknown as to when the material was removed. If it was never removed, then that may be part of the reason so many rats died prior to termination of the test. No information was submitted as to how much of the body surface area was shaved. It does not appear that this material is dermally irritating, however, the study can only be categorized as CORE SUPPLEMENTARY.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

EDB 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral - Rat (82-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151470

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): SU-SB-75.07.19/A

SPONSOR: Not given

TESTING FACILITY: Shinshu University Medical College, Japan

TITLE OF REPORT: The Results of Subacute and Chronic Toxicity Tests in the Rat (6 month study)

AUTHOR(S): I. Motoyama, T. Yanagidaira, A. [illegible]ai and T. Minakami

REPORT ISSUED: July, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-13

CONCLUSION: No statistically significant toxic effects were noted in any of the treated groups when compared to controls. NOEL: 0.3% in diet (males) and 0.15% in diet (females).

Classification: CORE SUPPLEMENTARY. See discussion.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l-allethrolone (95:5)
Description: Not given
Batch #(s), Other #(s): Not given
Purity: 95%
Source: Not given

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): male and female Wistar rats
Age: 4 weeks
Weight(s): Not given
Source(s): Shizuoka Prefecture Experimental Animal Agricultural Associatio[illegible]

3. Procedure:

a. Dietary Preparation (if applicable): Details not given

Frequency of preparation: Not given

Storage conditions: Not given

Stability Analyses: Not done

Homogeneity Analyses: Not done

Concentration Analyses: Not done

b. Basis For Selection of Dosage Levels:

Not given

c. Animal Assignment and Dose Levels: Two studies conducted concurrently (a 6-month feeding study and a 90-day study). Same dosage levels used.

Test Group	Dose Administered Percent in diet	Main Study - Either 6 Months or 90 Days male and female
Contr.	0	5 (90 days), 10 (6-month)
1	0.01 (male), 0.005 (female)	5 (90 days), 10 (6-month)
2	0.03 (male), 0.01 (female)	5 (90 days), 10 (6-month)
3	0.1 (male), 0.03 (female)	5 (90 days), 10 (6-month)
4	0.3 (male), 0.15 (female)	5 (90 days), 10 (6-month)

d. Procedures for Studies Other Than Feeding and/or Additions, Changes in Feeding Study: None

e. Clinical Observations and Mortality: Twice daily

f. Body Weight Determinations: Daily, days 1-10; every 10 days thereafter (90-day study), every 20 days thereafter (6-month study)

g. Food and/or Water Consumption: When animals weighed

h. Ophthalmological Examinations (if applicable): Not done

i. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals):
At completion of either 90-day or 6-month study

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*		Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*		Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*		
	Platelet count*		
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*	x	Cholesterol*
	Potassium*		Globulins
	Sodium*	x	Glucose*
	Enzymes:		Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
	Creatinine phosphokinase*	x	Protein fraction
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		

3) Urinalysis:

Collection times for urine (including # of animals):
At completion of 6-month study.

The following CHECKED (X) parameters were examined:

X		X	
	Appearance*		Glucose*
	Volume*		Ketones*
	Specific gravity*		Bilirubin*
	pH		Blood*
	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

j. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

No deaths or sacrifices prior to termination of studies.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

All animals.

k. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

None.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

90-day study: 4 controls/sex, 3 mid-dose animals/sex, 2 high dose animals/sex. 6-month study: 7 controls/sex, 5 mid-dose animals/sex, 3 high dose animals/sex.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		Aorta*	xx	Brain* (cerebrum, cerebellum)
	Salivary glands*	xx	Heart*		Periph. nerve*
	Esophagus*	x	Bone marrow*		Spinal cord (3 levels)*
	Stomach*		Lymph nodes*		Pituitary*
	Duodenum*	xx	Spleen*		Eyes (optic n.)*
	Jejunum* (x -intest.)	xx	Thymus*		Glandular
	Ileum*		Urogenital	xx	Adrenals*
	Cecum*	xx	Kidneys*		Lacrimal gland
	Colon*		Urinary bladder*		Mammary gland*
	Rectum*	xx	Testes*		Parathyroids*
xx	Liver*		Epididymides	x	Thyroids*
	Gall bladder*		Prostate		Other
x	Pancreas*		Seminal vesicle		Bone*
	Respiratory	xx	Ovaries		Skeletal muscle*
	Trachea*		Uterus*		Skin
xx	Lung*				All gross lesions and masses

l. Statistical Analyses: Not stated.

B. RESULTS:

1. Dietary Preparation: Not done

2. Clinical Observations and Mortality: No deaths in either study. No clinical signs related to treatment.

3. Body Weight Determinations: A slight inhibition of weight gain in the highest dose group (both male and female, 90-day). In 6-month study, inhibition of weight gain in males of highest dose group and slight

inhibition in second highest group. In females, slight inhibition in weight gain in both highest does levels. Differences not significant (not stated whether or not this applies to all groups).

4. Food and/or Water Consumption: No differences between control and treated groups (according to authors).

5. Ophthalmological Examinations: Not done

6. Hematology: No significant differences found (according to author, not known what statistics used).

7. Clinical Chemistry: In both studies, BUN was somewhat high in male high dose and in female 0.03 and 0.15% dose groups. In the 6-month study, the female 0.01% group was slightly high as well. The authors state that the values were all within normal limits. In the 6-month study, SGPT was somewhat high in the high dose males and females. The differences were not significant, however (according to author).

8. Urinalysis: No differences noted.

9. Gross Pathology: No gross abnormalities observed.

10. Organ Weights: No significant differences between dosed and treated groups in either study.

11. Histopathology:

    a. Nonneoplastic lesions: No changes related to treatment were noted.

    b. Neoplastic lesions: No changes related to treatment were noted.

12. Quality Assurance Measures: Not done.

C. DISCUSSION:

This study is classified as CORE SUPPLEMENTARY. The following list gives some of the reasons:

1. Although some information can be obtained from the studies (a 6-month and a 90-day study) histopathology examinations were conducted on too few animals (at the most, 7/10 control animals of each sex, 5 animals of each sex from the intermediate dose levels and 3 of each sex from the highest dose level).

2. No dietary analyses were conducted.

3. Hematology and clinical chemistry studies were only conducted at termination of the studies. No baseline data was obtained.

4. No ophthalmological examinations were conducted.

5. The following organs that have been suggested for histopathological examinations in the Guidelines were not examined: pituitary, parathyroid (thyroid was examined, so this may have been included), salivary glands, uterus, aorta, esophagus, stomach, urinary bladder, lymph node and peripheral nerve. In addition, it is unknown as to which sections of the intestine were examined.

6. It is unknown as to what statistical analyses were conducted. The data could not be verified.

Reviewed by: Pamela Hurley
Section 2 , Tox Branch (TS-769C)
Secondary Reviewer Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

82-4 (rat mouse)

DATA EVALUATION REPORT

STUDY TYPE: Inhalation - Subacute (1 month) - Rats and Mice

TOX. CHEM. NO.: 25A

ACCESSION NUMBER Not given MRID NO. 00151467

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): OU-SB-75.05 27/A

SPONSOR: Not given

TESTING FACILITY: Central Research Laboratory, Japan Mosquito Coil Co., Ltd.

TITLE OF REPORT: Esbiol Subacute Inhalation Toxicity Tests in the Mouse and Rat

AUTHOR(S): Y. Sakamoto, K. Matsumoto, H. Ogami, M. Yoshimura, N. Sano and T. Shimada

REPORT ISSUED: May 27, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-10

CONCLUSION: This study is classified as CORE SUPPLEMENTARY. The animals were exposed to an aerosol of the substance for periods of 2 hours/day, 6 days/week for one month. No particle size analyses were conducted so that it was unknown as to what particle sizes the animals were being exposed to. Esbiol was dissolved in deotomisol at concentrations of 0.5%, 2.5% and 5% and tested in the animals as an aerosol. The results indicated that clinical signs of toxicity included excitation, tail raising, jumping, salivation and slight trembling in the mouse, and slight salivation and nasal hemorrhaging in the rat in the 2.5% and 5.0% groups. One female mouse in the 2.5% group and 4 female mice in the 5% group died. No significant histopathological changes were noted in these animals when compared to controls. No other signs of toxicity were noted. The clinical signs of toxicity in mice were observed daily during exposure and some continued after completion of exposure, but not during the next day. In rats, the nosebleeds and salivation disappeared after 3 weeks.

83-3 (rat)

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Rats (83-3) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151471

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S) CP-SB-75 02 28/A

SPONSOR: Not given

TESTING FACILITY General Research Laboratory Chugai Pharmaceutical Co . Ltd

TITLE OF REPORT: Esbiol Teratological Tests Results in Rats and Mice

AUTHOR(S): N. Shioda, O Sugiyama Y Takagaki

REPORT ISSUED: February 1975

IDENTIFYING VOLUME Volume 5 of 5 Tab SBA-14

CONCLUSION: Under the conditions of the study it appears that Esbiol is not teratogenic at the dose levels tested. Maternal toxicity NOEL 0.025 ml/kg Fetotox NOEL 0.1 ml/kg

Classification: CORE SUPPLEMENTARY. See discussion

A. MATERIALS AND METHODS

1 Test Compound(s)

Chemical Name: d-trans chrysanthemic acid of d,l, allethrolone (95:5)
Description: Oily liquid with a high specific gravity
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Olive oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Wistar-Imamichi rats
Age: Mature male and female rats
Weight(s): 270g (female rats)
Source(s): Experimental Animal Center of Research Laboratory

3. Procedure:

A preliminary study was conducted with mature male and female rats and with pregnant rats in order to determine the dosages to be used in the main study. Esbiol was diluted with olive oil using two dilution ratios, a 20x dilution and a 40x dilution. All the test groups were dosed by gavage, once per day for 6 days (days 9-14 of the pregnant rats). The male rats were dosed orally with 0.1, 0.2 and 0.4 ml/kg Esbiol (20x dilution) and with 0.1, 0.2, 0.4 and 0.8 ml/kg Esbiol (40x dilution). The female rats were dosed with 0.025, 0.05 and 0.1 ml/kg Esbiol (20x dilution) and with 0.05, 0.1, 0.2 and 0.4 ml/kg Esbiol (40x dilution). The pregnant rats were dosed with 0.2 and with 0.1 ml/kg Esbiol (20x dilution) and with 0.2 ml/kg (40x dilution). Six-day oral LD_{50}'s were estimated from these preliminary test results. Based upon results from the preliminary study, the following dose levels were selected for the main study: 0.025, 0.05 and 0.1 ml/kg Esbiol (40x dilution). Control animals received 4 ml olive oil per kg body weight.

Mature young healthy female rats were selected for the main part of the study. They were confirmed to have undergone at least 2 sexual cycles. The females were placed together with mature male rats of the same strain in the evening. The following morning they were examined for the presence of sperm in the vagina. This day was considered to be day 0 of pregnancy. The following numbers of pregnant animals were tested: 0.2 ml/kg (prelim. study) - 11, 0.1 ml/kg - 22, 0.05 ml/kg - 23, 0.025 ml/kg - 21 and 0ml/kg 21 animals. Esbiol was administered by gavage at the dose levels listed above on days 9-14 of pregnancy. Bodyweights of the dams were determined on the day of mating and on days 3, 6, 9-15, 18 and 21 of pregnancy. They were observed daily for clinical signs of toxicity. On day 21, the dams were sacrificed by cervical dislocation and grossly examined. The following organs weights were measured: liver, spleen, kidneys, ovaries, adrenals, thymus, pituitary, uterus and intestine (stomach to rectum). The viable fetuses were given external examinations, killed by ether anesthesia and given internal gross examinations (no details given). The following observations were recorded: number of implantation sites, embryonic and fetal deaths and viable fetuses; the sex of the fetuses; the viable fetus weights and placenta weights; external abnormalities and skeletal abnormalities. In addition, the death rate, sterility rate (% which did not conceive) and pregnancy maintenance rate (% which did not abort) were recorded for the dams in each dose level.

B. RESULTS:

1. Maternal Toxicity

Death rate, sterility rate and pregnancy maintenance were similar for controls and all treated groups in the main study. At a dose level of 0.2 ml/kg used in the preliminary study, death rate was significantly elevated and pregnancy maintenance rate was significantly depressed (if compared to controls from the main study). Sterility rate was similar to that found in the main study for all groups. Clinical signs of toxicity appeared in almost all the dams at the 0.1 ml/kg dose level. Tremors, salivation, piloerection, blood-like discharge from the eyes and increased

hypersensitivity to sound stimulus were observed in these animals 1 to 2 hours following dosing. The tremors disappeared 2-4 hours following the initial dose, but became more marked as the number of times of dosing increased. One animal from the 0.1 ml/kg group died on day 6 and one animal from the 0.05 ml/kg group died on day 2. Hypertrophy of the liver, roughness of the liver parenchyma and congestion of the brain and heart were noted in these animals upon autopsy. The results of the preliminary test with the pregnant rats dosed at the 0.2 ml/kg level were mixed in with the results from the main study. Bodyweight gain was not inhibited in any of the treated groups (except in the 0.2 ml/kg group when included with the main study results). No significant differences in the organ weights of any of the treated groups were noted (except in the 0.2 ml/kg group which indicated atrophy of the thymus).

In all of the dosed groups used in the main study, there were no significant differences in the treated animals versus the controls with respect to number of implantations, number of viable fetuses, frequency of embryonic (fetal) death, lethality with respect to sex or placental weight. There was a tendency towards inhibition of viable fetal body weight with increasing dose, however, the differences were not statistically significant with respect to the control group. There were no external abnormalities in any of the groups in the main study. In the preliminary study, one dam in the 0.2 ml/kg group had 1 fetus with cleft palate and 7 with a reduced number of digits. The report only contained 1 summary table on skeletal abnormalities. The table listed total number of fetuses with abnormalities/dose level and the number of fetuses with either cervical, thoracic or lumbar abnormalities/dose level. The abnormalities included incomplete ossification of certain vertebrae, fusions of certain vertebrae, asymmetry and transformation of lumbar into thoracic vertebrae. One variation which appeared to increase with increasing dose was transformation of lumbar vertebrae to thoracic vertebrae: (45/230 (control), 48/227 (0.025), 66/222 (0.05), and 104/246 (0.1 ml/kg)). The authors stated, "In consideration of the frequency and severity of each type of abnormality, and the fact that compounded skeletal abnormalities, with the exception of compounded abnormalities of a variant formation, only occurred in 1 fetus (0.2 ml/kg group, preliminary study: fusion of the right 1st and 2nd thoracic vertebral arch + fusion of the 11th and 12th ribs), Esbiol does not appear to have a particularly great great effect on the process of skeletal formation in the fetus." In examining the data, it appears that the authors may be correct in their conclusions, however, one table is insufficient in order to verify their statement.

C. DISCUSSION:

This study had a number of problems. The following is a list of questions and/or deficiencies:

1. Results from the preliminary study were mixed in the the results from the main study. This is not good science and should not be done. Results from two separate studies conducted at two different times should not be compared. There are too many variables involved.

2. The pregnant animals were only dosed from day 9 to 14. The Guidelines

state that they should be dosed from days 6-15. Dosing from days 9-14 may cause some important data to be missed.

3. There were no details as to how the soft tissue examinations were conducted. There were no tables on soft tissue examinations either. Someone reviewing the study would not know what was examined and what was not.

4. There was no indication that the investigators examined the heads. This is important. An observed cleft palate in the gross external examination should have been verified by a skeletal abnormality. It was not mentioned.

5. There were no details in the skeletal abnormality tables. One cannot tell which fetuses were examined for what abnormality or whether or not one fetus had multiple abnormalities. The table is insufficient.

6. Corpora lutea were not counted. This is necessary in order to tell whether or not there were any pre-implantation losses (although it is not likely that this would have happened in this case because the dosing was started so late).

This study is classified as CORE SUPPLEMENTARY since some information can be obtained from it, although it is not adequate as a teratology study.

Reviewed by Pamela Hurley
Section 2 . Tox Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

4/23/87

83-3 (mouse)

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Mice (83-3) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO.: 00151471

TEST MATERIAL: Esbiol

SYNONYMS: S-Bioallethrin

STUDY NUMBER(S): CP-SB-75.02.28/A

SPONSOR: Not given

TESTING FACILITY: General Research Laboratory, Chugai Pharmaceutical Co., Ltd.

TITLE OF REPORT: Esbiol Teratological Tests Results in Rats and Mice

AUTHOR(S): N. Shioda, O. Sugiyama, Y. Takagaki

REPORT ISSUED: February, 1975

IDENTIFYING VOLUME: Volume 5 of 5, Tab SBA-14

CONCLUSION: Under the conditions of the study, it appears that Esbiol is not teratogenic at the dose levels tested. Maternal toxicity NOEL could not be established. Fetotox. NOEL 0.1 ml/kg (HDT in main study).

Classification: CORE SUPPLEMENTARY. See discussion.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d,l, allethrolone (95:5)
Description: Oily liquid with a high specific gravity
Batch #(s), Other #(s): Not given
Purity: Not given
Source: Not given
Vehicle (if applicable): Olive oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Tvcs mice
Age: Mature males and 80-100 day old females
Weight(s): 25-30 grams (females)
Source(s): Experimental Animal Center of Research Laboratory

3. Procedure:

A preliminary study was conducted with pregnant mice in order to determine the dosages to be used in the main study. Esbiol was diluted with olive oil using 3 dilution ratios, a 10x dilution, a 50x dilution and a 100x dilution. The animals were dosed by gavage, once per day for 6 days (days 7-12 of the pregnant mice). Each dilution ratio was tested with either one or two doses of undiluted Esbiol : 1.0 and 0.5 ml/kg Esbiol (10x dilution), 0.1 ml/kg Esbiol (50x dilution) and 0.2 and 0.1 ml/kg Esbiol (100x dilution).

Based upon results from the preliminary study, the following dose levels were selected for the main study: 0.05 and 0.1 ml/kg Esbiol (100x dilution).

Mature young healthy female mice were selected for the main part of the study. They were confirmed to have undergone at least 1 sexual cycle. The following numbers of females were used: 5(0.2 ml/kg), 29(0.1 ml/kg), 29(0.05 ml/kg) and 23 (controls). The females were placed together with mature male mice of the same strain in the evening. The following morning they were examined for the presence of a vaginal plug. This day was considered to be day 0 of pregnancy. Esbiol was administered by gavage at the dose levels listed above on days 7-12 of pregnancy. Bodyweights of the dams were determined on the day of mating and on days 3, 6-13, 15 and 18 of pregnancy. They were observed daily for clinical signs of toxicity. On day 18, the dams were sacrificed by cervical dislocation. The viable fetuses were given external examinations, killed by ether anesthesia and given internal gross examinations (no details given). The following observations were recorded: number of implantation sites, embryonic and fetal deaths and viable fetuses; the sex of the fetuses; the viable fetus weights and placenta weights; external abnormalities and skeletal abnormalities. In addition, the death rate, sterility rate (animals for which implantation sites were not observed) and abortion rate were recorded for the dams in each dose level.

B. RESULTS:

1. Maternal Toxicity:

The results from the preliminary study were combined with the results from the main study. No deaths occurred in the control and 0.05 ml/kg groups (0/23 and 0/29, respectively). Two of 29 animals died in the 0.1 ml/kg group and 2/5 animals died in the 0.2 ml/kg group (from the preliminary study). Clinical signs of toxicity (tremors) occurred in the two top dose levels. There was a tendency towards increased abortion and sterility rate in all the treated groups. The authors state that they were not statistically significant when compared to controls, however, they appear to be biologically significant. There were no differences in body weight gains between the groups. Very little data was presented to support these statements.

2. Embryo/Fetotoxicity:

There were no differences between the control and treated groups with respect to average number of implantations, the incidence of embryonic/fetal deaths, the average number of viable vetuses, fetal body weight and sex ratios, and the average weight of the placenta. One fetus with cleft palate and hydrocephalus and 1 with cleft palate alone were observed out of 229 fetuses in the 0.1 ml/kg group. In the control group, 1 fetus with an abdominal hernia and 1 fetus with hydrocephalus were noted out of 207 fetuses. No skeletal malformations were noted that appeared to be related to treatment with Esbiol. The types of skeletal abnormalities observed were insufficient ossification of occipital bone (1/207 controls and 1/229 high dose group), separation of left and/or right 1st vertebral arch (3 controls, 6/196 mid-dose, probably 3 high dose group, one number omitted), either left and right asymmetry of the sternum (1 each control and high dose) and incomplete ossification of the 5th sternum (2 mid-dose).

C. DISCUSSION:

This study had a number of problems. The following is a list of questions and/or deficiencies:

1. Results from the preliminary study were mixed in the the results from the main study. This is not good science and should not be done. Results from two separate studies conducted at two different times should not be compared. There are too many variables involved.

2. The pregnant animals were only dosed from day 7 to 12. The Guidelines state that they should be dosed from days 6-15. Dosing from days 7-12 may cause some important data to be missed.

3. There were no details as to how the soft tissue examinations were conducted. There were no tables on soft tissue examinations either. Someone reviewing the study would not know what was examined and what was not.

4. There were no details in the skeletal abnormality tables. One cannot tell which fetuses were examined for what abnormality or whether or not one fetus had multiple abnormalities. The table is insufficient.

5. Corpora lutea were not counted. This is necessary in order to tell whether or not there were any pre-implantation losses (although it is not likely that this would have happened in this case because the dosing was started so late).

6. In general, too little information was supplied on the procedures used for the study and too little data were supplied in reporting the results. Therefore, the results could not be verified by the scanty information supplied.

This study is classified as CORE SUPPLEMENTARY since some information can be obtained from it, although it is not adequate as a teratology study.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

Budd 4/23/87

DATA EVALUATION REPORT

STUDY TYPE: Acute oral toxicity - rat (81-1) TOX. CHEM. NO.: 25A

ACCESSION NUMBER: Not given MRID NO: PHES0001

TEST MATERIAL: Esbiothrin

SYNONYMS: None

STUDY NUMBER(S): RU-EBT-79828/A

SPONSOR: Roussel Uclaf, Romainville, France

TESTING FACILITY: Toxicology Dept., Roussel Uclat. 102-109, Route de Noisy-le-Sec 93230 Romainville, France

TITLE OF REPORT: Esbiothrin. Acute Oral Toxicity Study in the Rat

AUTHOR(S): L. Audegond, E. Collas and R. Glomot

REPORT ISSUED: November 5, 1979

IDENTIFYING VOLUME: Volume 3 of 5, Tab EBT-1

CONCLUSION: Oral LD_{50} for males in PEG 200 is 432.3 mg/kg (270.5-728.3 mg/kg) and LD_{50} for females is 378.0 mg/kg (219.3-555.6 mg/kg).

Toxicity Category: II

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: d-trans chrysanthemic acid of d-allethrolone (72%) and d-trans chrysanthemic acid of l-allethrolone (21%)
Description: Not given
Batch #(s), Other #(s): 9 L 1069
Purity: Not given
Source: Not given (assumed Roussel Uclaf)
Vehicle (if applicable): Polyethyleneglycol 200

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female CD1 Sprague Dawley rat
Age: Not given
Weight(s): 100-110 grams
Source(s): IFFA CREDO breeding colony, 69210 St. Germain Sur L'Arbresle, France

3. Common Name: S-bioallethrin

   Trade Name: Esbiol Concentrate

   Shaugnessy Code: 4004

   Active Ingredient: 90% Allyl homolog of Cinerin I and 5% other allethrin stereoisomers

4. Common Name: d-cis/trans allethrin

   Trade Name: Pynamin-Forte

   Shaungnessy Code: 4005

   Active Ingredient: 36.5% Allyl homolog of Cinerin I and 55.5% other allethrin stereoisomers

5. Common Name: Esbiothrin *

   Trade Name: Esbiothrin

   Shaugnessy Code: 4003 + 4004

   Active Ingredient: 72% Allyl homolog of Cinerin I and 21% other allethrin stereoisomers

* This product in the allethrin series is a combination of two products, 60% Esbiol (s-bioallethrin, No. 3) and 40% Bioallethrin (No. 2). This product has been approved for use in conducting chronic toxicity studies to satisfy the data requirements imposed by a Data Call-In Notice for Allethrin and all isomers. See Attachment II.

At the first support team meeting for the Bioallethrin Registration Standard held on November 7, 1986, it was unanimously agreed that the proposed standard should cover all of the above five technical/manufacturing use allethrin products unless a scientific rationale could be provided why any should be excluded from the standard. The Toxicology Branch (TB) representative was asked to consider the proposal to include all of these products in one registration standard. If any of these products should not be included in the standard, a scientific rationale should be provided to justify why it should be excluded.

McLAUGHLIN
GORMLEY
KING
8810 Tenth Ave. North
Minneapolis, Minnesota 55427, U.S.A.
Area Code 612-544-0341

TECHNICAL BULLETIN

ATTACHMENT I

SBIOTHRIN(R)

from

McLAUGHLIN GORMLEY KING COMPANY

A Pyrethroid for Domestic, Industrial
and Public Health Use

This bulletin adapted from Roussel Uclaf ESBIOTHRIN® bulletin dated July, 1979

® Registered Trade Mark Roussel Uclaf - Paris November, 1979

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

FE: 4 15.

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA #004001. Response to the Roussel Uclaf Proposal Concerning Testing One Allethrin Formulation as a Representative for Several Others

TO: Susan Lewis, PM Team #50 Tox. Chem. No. 25
Registration Division (TS-767c)

FROM: Pamela Hurley, Toxicologist Pamela M. Hurley
Toxicology Branch
Hazard Evaluation Division (TS-769c)

THROUGH: Edwin Rudd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769c)

Rudd 2/3/86

I.D. No. 004001
Record Nos. 158,429; 159,037 and 160,241

W.D. Burnam 2-4-86

Action Requested and Background:

During the summer of 1985, the Toxicology Branch was requested to respond to a proposal submitted by Roussel Uclaf, dated June 11, 1985. The proposal concerned a data call-in notice on three allethrin formulations. The formulations contained identical chemical products except that the percentage of each product in each formulation was different. The data call-in notice required testing all three of the formulations for chronic, reproductive and oncogenic effects. Roussel Uclaf submitted a request, accompanied by a rationale, for testing one of the formulations as a representative for all three. At that time, in order to facilitate a decision concerning the proposal, the Toxicology Branch asked for the company to submit all the subchronic, chronic, reproductive, teratogenic and other relevant data already available on the three formulations. In addition, other relevant data and papers were obtained from the EPA files as well. All of the data collected on the three formulations have been reviewed.

Response:

The Toxicology Branch has determined that the proposal to test Esbiothrin (EBT) in order to satisfy the data call-in requirements on the three formulations, Bioallethrin (BA), EBT and Esbiol (SBA) is acceptable.

Discussion:

BA, EBT and SBA each contain almost exclusively the two isomers, d-trans chrysanthemate ester of d-allethrolone (d-isomer) and d-trans chrysanthemate ester of l-allethrolone (l-isomer). The relative ratios of these two isomers expressed as (d:l) are respectively

50:50 for BA
77:23 for EBT
95:5 for SBA

An analysis of the existing data on the three formulations indicates that in oral studies, each affects the same target organs, particularly the liver. Although the acute oral studies indicate that the d-isomer appears to be more acutely toxic than the l-isomer, the subchronic studies indicate that the NOEL's and the LOEL's for BA and SBA are similar (no subchronic data were available for EBT). In addition, subchronic data were available for Pynamin and Pynamin Forte. These two formulations are similar to the other three except that the chrysanthemate portion of the molecules are cis/trans instead of only trans. The data on these two formulations also indicate similar NOEL's and LOEL's.

The rationale submitted by Roussel Uclaf also contains information concerning the chemistry and syntheses of the formulations and a list of inerts and impurities. This information also supports testing only EBT to satisfy the data call-in requirements for all three formulations.

Attachment

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

NOV 12 1986 OFFICE OF S AND TOXIC SUBSTAN

MEMORANDUM

SUBJECT: Bioallethrin Registration Standard: Selection of Isomers To Be Included in the Standard

TO: Richard King, PM Team #17 Tox. Chem. No. 25A
Insecticide-Rodenticide Branch
Registration Division (TS-767c)

FROM: Pamela Hurley, Toxicologist Pamela M. Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c) 11/12/86

Robert Zendzian, Registration Standard
Coordinator, Toxicology Branch
Hazard Evaluation Division (TS-769c) 11/12/86

William L. Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769c) 11/12/86

Background:

On November 30, 1984 and February 21, 1985 the Agency sent out a data call-in notice for allethrins, which included products which contained different ratios of allethrin isomers. The toxicologic data required included chronic feeding studies in 2 species, oncogenicity studies in 2 species and a reproduction study in 1 species. Because of the differences in isomeric ratios in allethrin products, the Agency proposed that the registrants confer with one another to consider appropriate test material(s) for the long term studies required to support continued registration. In response to the data call-in notice, Roussel Uclaf, a manufacturer of allethrin products, sent a proposal to the Agency which requested testing Esbiothrin (EBT) as a representative to satisfy the testing requirements for 3 products, Bioallethrin (BA), EBT and Esbiol (SBA). The Toxicology Branch (TB) considered the proposal and in a memorandum to S. Lewis on February 4, 1986, TB accepted it. Roussel also stated that they plan to stop manufacturing a fourth product, Allethrin (Pynamin).

A second manufacturer of allethrin products, Sumitomo Chemical Company, responded to the notice with a letter stating that they would be testing a third product, Pynamin Forte with all the required studies.

Other companies which have responded to the data call-in notice thus far have been formulators for Allethrin (Pynamin) products. These companies have requested formulators' exemptions. At the present time, the Agency is unclear as to whether or not there are any other manufacturers for technical Allethrin (Pynamin) except possibly Sumitomo, which to TB's knowledge has not stated its intentions concerning testing this product. The Agency is in the process of sending out another notice on Allethrin, stating that the date has expired for replies to the call-in notice for technical Allethrin.

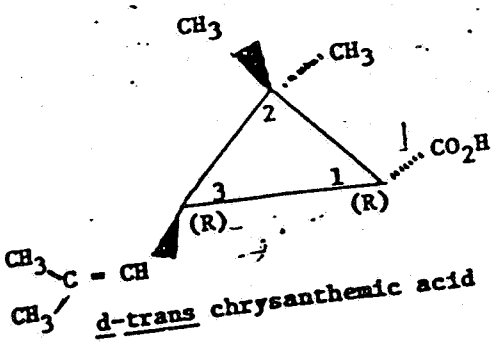
At the first support team meeting for the Bioallethrin Registration Standard, the issue came up as to whether or not the five products, Allethrin, Pynamin Forte, Bioallethrin, Esbiothrin and Esbiol should all be included in the Standard. The Toxicology Branch was asked to consider the proposal to include all these products.

Response:

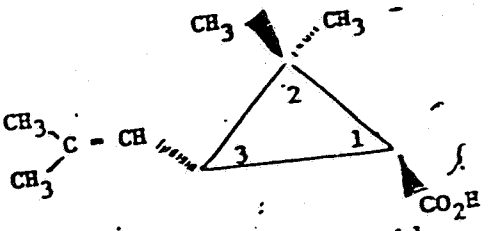
TB has decided to include only Bioallethrin, Esbiothrin and Esbiol in the Standard because TB has already accepted Roussel's proposal to test Esbiothrin as a representative for Bioallethrin and Esbiol (memorandum mentioned in background section), Pynamin Forte is already being tested separately by Sumitomo, and because there is a possibility that Technical Allethrin may be dropped by the manufacturers of Allethrin (Pynamin). TB believes that including all of the 5 mentioned allethrin products in the Registration Standard would only confuse the Registrants who are at the present time testing their products separately.

CHEMICAL STRUCTURE OF ALLETHRIN ISOMERS

ACID



d-trans chrysanthemic acid



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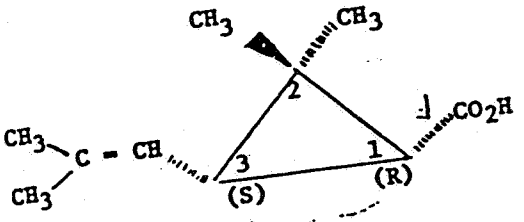
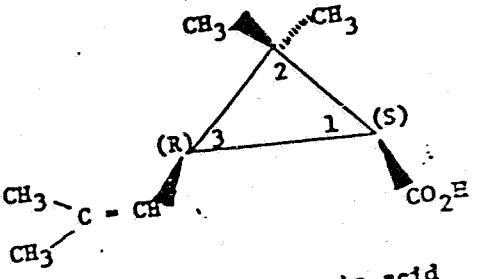
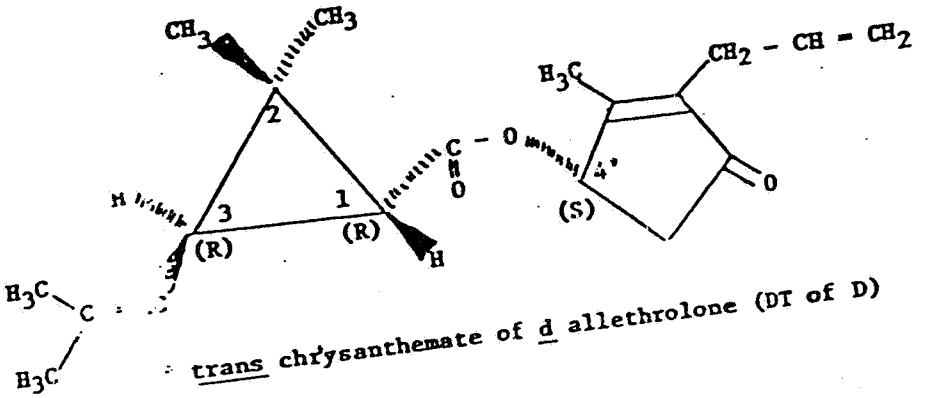


d-cis chrysanthemic acid



l-cis chrysanthemic acid

ESTERS



trans chrysanthemate of d allethrolone (DT of D)

The specifications of Esbiothrin EBT 60/40 are given in Table II.

TABLE II: ESBIOTHRIN SPECIFICATIONS

Appearance:	Orange-Brown viscous oil
Optical Rotation:	$[\alpha]_D$ (C = 5% toluene) higher or equal to -37.5°
Assay:	Higher or equal to 93%
Chrysanthemic Acid Chloride:	Less than 0.2%
Free Chrysanthemic Acid + Chrysanthemic Anhydrate:	Less than 4%

The method of analysis to be used is the one applicable to Esbiol.

These specifications correspond to a content of:

d-trans chrysanthemate of d allethrolone $\geqslant$72%

II. TOXICOLOGICAL DATA-METABOLISM

The toxicological properties of Esbiothrin EBT 60/40 correspond to the ones of Bioallethrin and Esbiol which are in fact very similar.

Table III gives the basic acute oral toxicity data available in the rat (Wistar rats for Bioallethrin, Esbiol and Sprague Dawley rats for Esbiothrin).

TABLE III: ACUTE ORAL TOXICITY OF BIOALLETHRIN, ESBIOTHRIN AND ESBIOL IN THE RAT

Species	Sex	Product	Solvent	Confidence limits for LD 50 in mg/kg	Origin of the study
Rat (Wistar)	Male	Bioallethrin	PEG 200	550 - 870	RU 1972
Rat (Wistar)	Male	Esbiol	PEG 200	617 - 951	RU 1972
Rat (Sprague Dawley)	Male	Esbiothrin	PEG 200	507 - 1063	RU 1978

Species	Sex	Product	Solvent	Confidence limits for LD50 in mg/kg	Origin the Str
Rat (Wistar)	Female	Bioallethrin	PEG 200	508 - 742	
Rat (Wistar)	Female	Esbiol	PEG 200	531 - 829	RU 1977
Rat (Sprague Dawley)	Female	Esbiothrin	PEG 200	321 - 500	RU 1978

It may be worthwhile to call the readers attention to some of the additional toxicological data available for Bioallethrin and Esbiol with other species.

-mouse acute oral LD 50	in the range of	300 to 400 mg/kg
-rabbit acute oral LD 50	in the range of	2000 mg/kg
-dog acute oral LD 50	higher than	1000 mg/kg

Long term (90 or 180 days) feeding studies and metabolic studies have also confirmed that allethrin derivatives such as Bioallethrin and Esbiol (and therefore Esbiothrin) present no hazard when used at recommended levels in aerosols, sprays, coils, mats, etc.

III. BIOLOGICAL ACTIVITY: SYNERGISTIC EFFECT

By its composition, Esbiothrin EBT 60/40 is closely connected with Bioallethrin and Esbiol in which the only allethrin isomers present are the DT of D and the DT of L, the former being by far the most active one.

As a first approach based on the composition, it may therefore be expected that Esbiothrin is close to 1.6 times more active than Bioallethrin, while Esbiol is some 1.95 times more active. Recent studies have, however, demonstrated that by changing the stereoisomer composition, the physicochemical properties are modified, and consequently the biological activity against the insects may be different and superior to those expected. More specifically, the following results demonstrate a synergistic effect in coils between the DT of D and the DT of L isomers against mosquitoes and flies.

TABLE IV: ESBIOTHRIN VS. BIOALLETHRIN ACTIVITY IN COILS AGAINST C. pipiens. Concentration and relative potency at KT 50 of 7'.

Product	Concentration in Coils	Relation Potency
Bioallethrin	0.210	100
Esbiothrin	0.102	206

TABLE V. ESBIOTHRIN VS. BIOALLETHRIN ACTIVITY IN COILS AGAINST *A. aegypti*. Concentration and relative potency at KT 50 of 7.5'.

Product	Concentration in Coils	Relative Potency
Bioallethrin	0.155	100
Esbiothrin	0.070	[illegible]

TABLE VI: ESBIOTHRIN VS. BIOALLETHRIN ACTIVITY IN COILS AGAINST *M. domestica*. Concentration and relative potency at KT 50 of 13'.

Product	Concentration in Coils	Relative Potency
Bioallethrin	0.600	100
Esbiothrin	0.295	203

From these biological findings, it may be concluded that the higher content of DT of D in Esbiothrin enhances all activities higher than expected when taking only into consideration the relative DT of D content.

III. Continued - Tests from McLaughlin Gormley King Laboratories, U.S.A.

Shown in Table VII are results against houseflies that confirm the higher biological activity of Esbiothrin EBT 60/40 over Bioallethrin.

TABLE VII: Results With Water-Base Pressurized Sprays Against *M. domestica*, F-58WT-II Strain, by the CSMA Aerosol Test Method - 3g/1000 cu. ft. dosage.

% Active Ingredient	Avg. % Aerosol Test Knockdown 5 Min.	10 Min.	15 Min.	Avg. % ATKD Mortality 24 Hrs.
0.2 Esbiothrin 0.6 Piperonyl butoxide 1.0 MGK-264 8.2 Petroleum Dist.	26	46	68	48
0.3 Bioallethrin 0.6 Piperonyl butoxide 1.0 MGK-264 8.2 Petroleum Dist.	27	47	69	52
Official Test Aerosol*	23	[illegible]	57	52

Shown in Table VIII are results against German cockroaches that also confirm the higher biological activity of Esbiothrin EBT 60/40 over Bioallethrin

TABLE VIII: Results With Water-Base Pressurized Sprays Against B. germanica by the CSMA Cockroach Aerosol Test Method - .84 g. dosage.

% Active Ingredient	Avg. % Dead & Moribund 24 Hrs.	48 Hrs.
0.2 Esbiothrin 0.6 Piperonyl butoxide 1.0 MGK-264 8.2 Petroleum Dist.	99	99
0.3 Bioallethrin 0.6 Piperonyl butoxide 1.0 MGK-264 8.2 Petroleum Dist.	99	99
Official Test Aerosol*	72	70

* 0.2% Pyrethrins + 1.6% Piperonyl butoxide + 18.2% Petroleum Distillate with Propellents 11 & 12.

Esbiothrin EBT 60/40, considered as a combination of Esbiol and Bioallethrin, represents an economically valuable consideration in the formulation of aerosols, sprays, coils or mats.

IV. CONCLUSION

Esbiothrin EBT 60/40 constitutes a new industrial combination in the allethrin series.

Chemically, it constitutes an improved Bioallethrin with a DT of D content nearly 1.6 times higher.

Biologically, the isomer ratio induces a synergistic effect allowing an improved activity over the one expected from the chemical composition.

Economically, Esbiothrin EBT 60/40 is a valuable material to be included in aerosol, coil and mat formulae.

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

JUN 19 [illegible]

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Addendum to Toxicology Chapter of the Bioallethrin Registration Standard

Tox. Chem. No. 25
Tox. Chem. No. 25A

TO: Richard King, PM Team #17
Insecticide-Rodenticide Branch
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THROUGH: Robert P. Zendzian, Ph.D. 6/18/87
Registration Standard Coordinator
Toxicology Branch
Hazard Evaluation Division (TS-769c)

William Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769c)

Attached are the Toxicology Summary Tables for Allethrin and for d-cis/trans Allethrin, both of which are to be included in the Bioallethrin Registration Standard. With the exception of a chronic/oncogenicity study in the rat for d-cis/trans Allethrin, there are no adequately conducted toxicity studies available on either of the technical products. The Toxicology Summary Tables summarize the generic data requirements for Allethrin and d-cis/trans Allethrin. A review of the rat chronic/oncogenicity study on d-cis/trans Allethrin is also attached along with a summary of the results from the study.

D-Cis/Trans Allethrin - Chronic/Oncogenicity Feeding Study in Rats

D-cis/trans allethrin did not prove to be oncogenic under the conditions of the study. The levels tested were 125, 500 and 2000 ppm. For chronic effects, the NOEL's were 6.6 mg/kg/day for females and 5.9 mg/kg/day for males (125 ppm), based upon decreased body weight gains and the presence of histiocyte "phagocyting" crystals in the livers of females and increased liver weights in males. The LOEL's were 24.5 mg/kg/day for males and 28.6 mg/kg/day for females (500 ppm). Other chronic effects noted in the study were possible increases in kidney weights in males at the high dose level and increases in liver weights in females at the high dose level.

DYNAMAC
CORPORATION

Final Report

Bioallethrin
Task 2: Residue Chemistry Chapter

Contract No. 68-02-4226

April 30, 1987

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

;//

BIOALLETHRIN

RESIDUE CHEMISTRY

Task 2

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BIOALLETHRIN

RESIDUE CHEMISTRY

TASK 2

INTRODUCTION

Allethrin (004001), allethrin coil (004002), bioallethrin (004003), S-bioallethrin (004004), and d-cis/trans allethrin (004005) are insecticides containing two or more of the eight stereoisomers which comprise the d-trans-chrysanthemum monocarboxylic ester of dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one; the Shaughnessy No. for each compound appears parenthetically. This document, though entitled "Bioallethrin", covers all of these Shaughnessy numbers.

Allethrin (004001) is federally registered for preharvest use on apples, beans, broccoli, Brussels sprouts, cabbage, cauliflower, celery, citrus, collards, endive, horseradish, kale, kohlrabi, lettuce, mustard greens, parsley, peaches, pears, peppers, radishes, rutabagas, spinach, tomatoes, and turnips. A Special Local Need (SLN No. FL780061) registration permits preharvest use in FL on alfalfa, clover, cucurbits, peas, sorghum, and sugarcane. Allethrin (004001) is federally registered for postharvest use on apples, blackberries, blueberries, boysenberries, cherries, crabapples, currants, dewberries, grapes, muskmelons, oranges, peaches, pears, pineapples, plums, and raspberries. Allethrin formulations are also variously registered as a stored commodity treatment on grain, dried fruit, and stored food, for direct uses on horses and ponies, and for treatments of pets, ornamental plants and forest trees, domestic dwellings, aquatic sites, livestock premises, mushroom houses, and food handling establishments. Allethrin coil (004002) is predominantly used for outdoor control of adult mosquitoes.

The following formulations are registered for use on agricultural crops: the 0.9, 1, 2.5, and 15% emulsifiable concentrate (EC); the 2.5, 5, and 12.51% soluble concentrate/liquid (SC/L); and the 0.25 and 1.25% ready-to-use (RTU). Allethrin formulations registered for use in food handling establishments, livestock premises, and domestic dwellings include: the 1, 1.875, 2.5, 2.973, 3.4, and 15% emulsifiable concentrate; the 0.066, 0.31, 0.928, 1.394, 2, 5, and 12.51% soluble concentrate/liquid; the 0.0232, 0.0603, 0.163, 0.25, 0.326, 0.372, 0.5, and 1.25% ready-to-use; and the 0.025, 0.0603, 0.116, 0.125, 0.19, 0.197, 0.239, 0.422, 0.48, 0.5, 0.6, and 0.8 pressurized liquid (PrL). All formulations (EC, SC/L, RTU and PrL) may contain multiple active ingredients (MAIs). Allethrin formulations are applied foliarly by aerial or ground equipment to crops prior to harvest; postharvest applications are made as an emulsive dip. Formulations used in food handling establishments may be applied as a fogging treatment, space spray, or as a contact spray (surface, spot, crack and crevice treatment).

According to the Preliminary Quantitative Usage Analysis of Allethrin (R.P. Dates 1/87, BUD, OPP, EPA), bioallethrin (004003) accounts for 41.7-53.0%, D-cis/trans allethrin (004005) and allethrin (C04001) each account for 22.7-27.0%,

and S-bioallethrin (004004) accounts for 1.5-2.8% of the total estimated domestic usage. Household and structural (commercial and industrial) use sites account for 84.8-97.2% and 2.8-15.2%, respectively, of the total domestic usage of all the allethrin compounds.

Tolerances for residues of allethrin (allyl homolog of cinerin I) in food/feed items following posttreatment application are currently expressed in terms of allethrin per se (40 CFR 180.113). An exemption from the requirement of a tolerance for residues of allethrin (allyl homolog of cinerin I) in food/feed items following preharvest application is also currently expressed in terms of allethrin per se (40 CFR 180.1002).

NATURE OF THE RESIDUE IN PLANTS

Conclusions:

No data were submitted pertaining to the metabolism of allethrins in plants. The following data are required:

- The uptake, distribution, and metabolism of [^{14}C]allethrin in a tree fruit crop (pome, stone, or citrus), a legume or fruiting vegetable (beans or tomatoes) and a leafy or brassica leafy vegetable (lettuce or cabbage). [^{14}C]allethrin (004001 - a mixture of eight isomers) must be applied foliarly several times up to and including the day of harvest at rates sufficiently high to permit complete characterization of ^{14}C-residues. The identities and quantities of residues in or on mature plant parts must be determined in order to elucidate terminal residues. Representative samples from these tests must also be analyzed by enforcement methods to ascertain that the methods are adequately capable of quantifying all residues of concern.

Tolerances and exemptions from the requirement of tolerances are currently expressed in terms of allethrin per se (allyl homolog of cinerin I). Upon receipt of the above-requested data, the tolerance definition will be reevaluated.

For a depiction of the molecular structure of the various allethrin-containing compounds, refer to Table 1 on page 3.

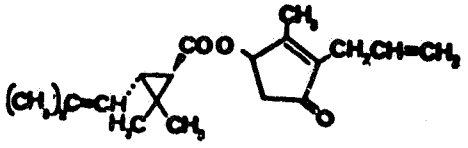
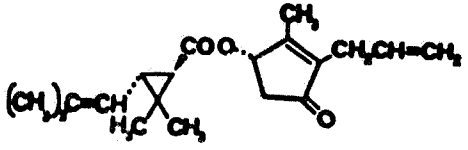
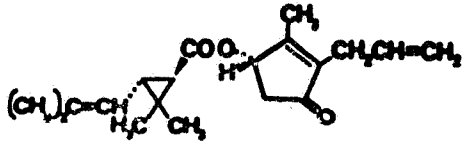
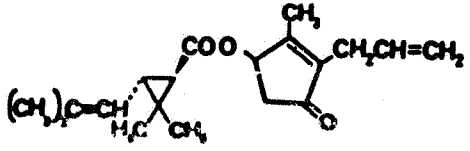
References (used):

N/A.

Discussion of the data:

N/A.

Table 1. Bioallethrin compounds.

Code	Structure	Chemical name	Common names
004001		cyclopropane carboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl-)-2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl ester (mixture of cis and trans isomers)	Allethrin; pynamin; allyl homolog of cinerin I
004003		d-trans-chrysanthemum monocarboxylic ester of dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one	Bioallethrin; d-trans allethrin
004004		d-trans-chyrsanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one	S-bioallethrin; esbiol
004005		d-cis/trans allethrin	d-allethrin; pynamin forte

NATURE OF THE RESIDUE IN ANIMALS

Conclusions:

No data were submitted pertaining to the metabolism of allethrin in animals. The following data are required:

- Metabolism studies utilizing ruminants and poultry. Animals must be dosed orally for a minimum of 3 days with [^{14}C]allethrin (004001 - a mixture of eight isomers) at a level sufficient to make residue identification and quantification in tissues and milk possible. Milk and eggs must be collected twice a day during the dosing period. Animals must be sacrificed within 24 hours of the final dose. The distribution and characterization of residues must be determined in milk, eggs, liver, kidney, muscle, and fat.

- Metabolism studies using cattle, poultry and swine reflecting direct animal treatment. These data are needed because allethrin (004001) is registered for use as a space spray in farm animal quarters and as a direct treatment to horses, and bioallethrin (004003) is registered for use as a space spray in milking houses. Animals must be sprayed daily for 28 days using [^{14}C]allethrin (004001 - a mixture of eight isomers) at a rate sufficiently high to permit complete characterization of ^{14}C-residues and sacrificed within one day of the final application. ^{14}C-Residues must be quantified and characterized in muscle, fat, liver, kidney, milk and eggs. Eggs and milk must be collected twice daily throughout the treatment period.

References (used):

N/A.

Discussion of the data:

N/A.

RESIDUE ANALYTICAL METHODS

Conclusions:

The available GLC methods (MRIDs 00031930 and 00064646) are adequate for collection of data pertaining to allethrin residues in or on raw agricultural and processed plant commodities. The former method has undergone a successful method trial (EPA memoranda by King Zee dated 9/11/80 and located in correspondence file for FAP#OH5265; no MRID assigned). The available colorimetric method (MRIDs 00035929 and 00135387) is inadequate for data collection because it is not sufficiently quantitative and recovery and validation data are lacking. A similar colorimetric method appears as method A in the Pesticide Analytical Manual (PAM), Vol. II.

The Residue Chemistry Data Requirements in 40 CFR 158.125(b)(15) require that regulated pesticide residues be subjected to one or more of the multiresidue procedures published in Appendix II of PAM Vol. I and available from the National Technical Information Service under Order No. PB 203734/AS. Allethrin is determined by Multiresidue Protocols I and III. Allethrin has been partially (50-80%) recovered through PAM I method 211.1/231.1 and completely (>80%) recovered through PAM I method 212.1/232.1 after Florisil cleanup.

Additional residue and validation data and appropriate methods may be required if requested metabolism/degradation studies reveal additional metabolites of toxicological concern. All residue data submitted in response to this Standard must be accompanied by a description of the analytical method used and method validation data (sensitivity, accuracy, and precision).

References (used):

MRIDs: 00031930. 00035929. 00064646. 00135387.

Zee, King. 1980. FAP#OH5265. Results of method trial for allethrin in food handling establishments. (No MRID assigned).

References (not used):

[The following MRIDs duplicate previously cited references or contain irrelevant information.]

MRIDs: 00031929. 00057240. 00089616.

Discussion of the data:

McLaughlin Gormley King Co. (19??; MRID 00031930) submitted a method for detection of allethrins in or on bread, butter, candy, lemon cream pie, meat, and potato. Analysis is by gas-liquid chromatography using electron capture detection (GLC/EC) and a column packed with 5% OV-1 on 80-100 mesh Chromosorb W(HP). The retention time for bioallethrin was 2.5 minutes. Descriptions of sample extractions are presented in detail in the following discussion; petroleum ether extracts from all samples are cleaned up on a Florisil column and the eluant is analyzed by GLC/EC.

Bread: Samples of bread are homogenized with Celite 545 and water: acetonitrile (10:90) and filtered. Residues in the filtrate are partitioned into petroleum ether with the addition of sodium chloride. The petroleum ether extract is washed with water, dehydrated by passage through anhydrous sodium sulfate, and reduced in volume by rotary evaporation.

Butter: Filtered butterfat samples are mixed with petroleum ether, partitioned into acetonitrile, then petroleum ether with addition of sodium chloride. The petroleum ether extract is washed with sodium chloride in an unspecified solvent, dehydrated, and concentrated.

Candy: Samples of candy are homogenized with heated (temperature unspecified) water:acetonitrile (35:65). Celite 545 is added with homogenization, and the mixture is filtered. Residues in the filtrate are partitioned into petroleum ether with sodium chloride. The petroleum ether extract is washed with water and dehydrated.

Lemon Cream Pie: Samples of pie are homogenized with Celite 545, water:acetonitrile (20:80, heated to an unspecified temperature) and filtered. Residues in the filtrate are partitioned into petroleum ether. The petroleum ether extract is washed with water and dehydrated.

Meat: Samples of meat are homogenized with anhydrous sodium sulfate (previously washed with petroleum ether), Celite 545, ethyl ether, and ethanol. Petroleum ether is added with homogenization, and the homogenate is decanted. Solid material remaining is extracted with petroleum ether. The petroleum ether extract is concentrated, and residues dissolved in petroleum ether are partitioned into acetonitrile, then petroleum ether with the addition of sodium chloride. The petroleum ether extract is washed with water and dehydrated.

Potato: Samples of potatoes are homogenized with Celite 545 and acetonitrile, and the homogenate is filtered. Residues in the filtrate are partitioned into petroleum ether with addition of sodium chloride. The petroleum ether extract is washed with water and dehydrated.

Recoveries of bioallethrin were 63-90% for bread; 73-80% for butter; 83-100% for candy; 87-93% for lemon cream pie; 70-99% for meat, and 90-110% for potato, each food was fortified with bioallethrin at 0.1-0.3 ppm. Recoveries from bread samples were: 80% for allethrin, 95% for d-cis/trans allethrin, 105% for S-bioallethrin and 85% for bioallethrin; samples were fortified with each compound at 0.2 ppm. Residues of bioallethrin in control samples were reported as follows: 0.002 ppm for bread; 0.005 ppm for butter; 0.005 ppm for candy; 0.006 ppm for lemon cream pie; 0.01 ppm for meat; and 0.004 ppm for potato. The stated limit of detection for the method is 0.1 ppm.

This GLC/EC method underwent a successful method trial (EPA memorandum by King Zee dated 9/11/80 and located in the correspondence file for FAP#OH5265; no MRID assigned). Recoveries from four samples each of bread and butter fortified with allethrin at 0.5 or 1 ppm were 90-100%. Control samples (two each) of bread and butter bore <0.01 ppm apparent allethrin residues.

McLaughlin Gormley King. Co. (19??, received 1980; MRID 00064646) submitted a GLC method for detection d-cis/trans allethrin residues in foods. Samples of apples, bread, butter, meat, potatoes, and sugar are extracted, purified, and analyzed by GLC using a column packed with 3% EiEff-3BP on 80-100 mesh Chromosorb W(HP) and a linear electron capture detector. Samples of apples, bread, or potatoes are homogenized in Celite 545 and acetonitrile. The

homogenate is filtered, and residues in the filtrate are partitioned into petroleum ether after addition of 2% NaCl. The aqueous layer is extracted with a second volume of petroleum ether and is discarded. The combined petroleum ether extract is washed with water. The organic phase is dehydrated by passage through anhydrous sodium sulfate and concentrated. The petroleum ether extract is applied to a Florisil column, activity specified only as "untreated, from reagent bottle." The petroleum ether eluates are discarded, and residues d-cis/trans allethrin are eluted in ethyl acetate:petroleum ether (5:95). Eluates are concentrated and then analyzed by GLC. Filtered butterfat samples are combined with petroleum ether in a separatory funnel, and residues are partitioned into four volumes of acetonitrile. Sodium chloride (2%) is added to the combined acetonitrile extract, and residues are partitioned into two volumes of petroleum ether. The combined petroleum ether extract is washed with two volumes of 2% NaCl, dehydrated by passage through anhydrous sodium sulfate, and concentrated for analysis by GLC following purification on a Florisil column, as previously described. Meat is homogenized in Celite 545, ethyl ether, and ethanol. Sodium sulfate-saturated petroleum ether is added, and the material is homogenized and filtered. All extracts are combined and evaporated at 50 C until the solvent is removed. The residue is dissolved in petroleum ether, partitioned into acetonitrile, and purified on a Florisil column as previously described. Sugar is dissolved in water, and residues are partitioned into petroleum ether. The petroleum ether extract is washed with water, dehydrated by passage through anhydrous sodium sulfate, and concentrated.

Recoveries for samples fortified with d-cis/trans allethrin at 0.1-0.6 ppm were 57-100% from 23 samples, including: 84-100% for three apple samples; 72-92% for three bread samples; 57-92% for eight butter samples; 75-83% for three meat samples; 80-97% for three potato samples; and 85-100% for three sugar samples. Apparent residues in or on a control sample for each food item were reported as <0.01 or "0" (undefined). The stated limit of detection for the method is 0.1 ppm.

FMC Corp. (1954; MRID 00035929 and 1956; MRID 00135387) submitted a colorimetric method developed by Schreiber and McClellan (1954) for determination of bioallethrin residues in wheat flour and meat and milk. This method is inadequate for collection of residue data pertaining to bioallethrins because it is not sufficiently quantitative. Residue data generated by this method are presented for informational purposes only and are inadequate to support tolerances or exemptions from tolerances based on currently registered uses. Both methods include sample extraction/partitioning in petroleum ether and reaction of concentrated acidified extracts with mercuric oxide:sulfuric acid:water reagent. Additional steps in extraction of flour included in MRID 00035929 are refluxing of petroleum ether extracts with ethanolic sodium hydroxide, addition of barium chloride, and partitioning into petroleum ether before reaction with the colorimetric reagent.

A modification of the Schreiber and McClellan colorimetric method authored by McClellan and Moore (1958; J. Agr. Food Chem. (6) 463-465) is method A in PAM Vol. II (Pesticide Reg. Sec. 120.113). This method is adequate for confirmatory purposes but is not sufficiently quantiative for purposes of data collection.

STORAGE STABILITY DATA

Conclusions:

No acceptable data have been submitted regarding the storage stability of allethrin residues in or on plant or animal commodities. The following data are required:

- o All residue data requested in this Standard must be accompanied by information specifying the storage intervals and conditions for samples analyzed. Data must also be submitted depicting the storage stability of the residues of concern under the same conditions and time intervals specified. In laboratory tests using fortified samples, the pure active ingredient and pure metabolites (if necessary) must be used. However, if field weathered samples are used, the test substance must be a typical end-use product.

References (used):

MRID: 00089450.

Discussion of the data:

Weevil-Cide Co. (1955; MRID 00089450) submitted a study depicting stability of allethrin residues in dust from an unspecified grain. Data were generated by an inadequate colorimetric method (1954; MRID 00035929) and are presented for informational purposes only. Samples of dust initially bearing residues of 0.22% allethrin were stored in direct sunlight (one sample) or in subdued light similar to bin storage (three samples). Residues generally declined in subsamples analyzed at monthly intervals for six months of storage. By 5 months, the sample incubated in light bore residues reported as "0.00%" (undefined limit of detection). Residues in samples after six months storage were "0.00%" and 0.07-0.09% following incubation under sunlight and subdued light, respectively.

MAGNITUDE OF THE RESIDUE IN PLANTS

Food/Feed Commodities Exempt from the Requirement of Tolerances

Field Grown and Greenhouse Crops

Tolerances:

The following crops are exempted from the requirement of tolerances for residues of allethrin (allyl homolog of cinerin I) when it is used before harvest: apples, artichokes (Jerusalem), beans, beets, beets (sugar), broccoli, Brussels sprouts, cabbage, carrots, cauliflower, celery, chicory, Chinese cabbage, citrus, collards, corn, endive, escarole, garlic, horseradish, kale, kohlrabi, leeks, lettuce, mushrooms, mustard greens, onions, parsley, parsnips, peaches, pears, peppers, potatoes, radishes, rutabagas, salsify, shallots, sorghum (milo), sorghum (grain), spinach, sweet potatoes, tomatoes, and turnips (40 CFR 180.1002).

Use directions and limitations:

The 1% EC formulation (004001) is registered for use on apples, citrus, peaches, and pears as a foliar application at 1 qt formulation/A in 200-600 gallons of water/A (applied by high volume ground equipment) or, for apples, peaches and pears only in 2-5 gal water/A (applied by low volume ground equipment). The 1% EC formulation (004001) is also registered as a foliar application at 1-1.5 pt formulation/A in 1-3 gal water/A to be applied using aerial equipment or low volume ground equipment on the following crops: beans, broccoli, Brussels sprouts, cabbage, cauliflower, celery, collards, endive, horseradish, kale, kohlrabi, lettuce, mustard greens, parsley, peppers, radishes, rutabagas, spinach, tomatoes, and turnips. The 2.5% EC-MAI formulation (004001) is registered for greenhouse or field use on beans, broccoli, Brussels sprouts, cabbage, cauliflower, collards, kale, lettuce, mustard greens, peppers, radishes, tomatoes, and turnips as a foliar application at 12-36 fl. oz formulation/100 gal water/A or at 1-3 tbsp. formulation/gal. No maximum number of applications or maximum seasonal use rate has been established, nor is there an established PHI.

Use of the 0.9% EC-MAI is permitted in FL under SLN No. FL780061 as a foliar application to alfalfa, apples, beans, broccoli, cabbage, cauliflower, celery, citrus, clover, cucurbits, kale, lettuce, peach, pear, peas, pepper, potato, sorghum, spinach, sugarcane, tomato, and turnip at 1-2 pt formulation in 1-3 gal/A. Applications may be repeated at 5- to 7-day intervals as needed using ground or aerial equipment. A 1-day PHI is in effect. [We note that alfalfa, clover, cucurbits, peas, and sugarcane do not appear in the commodity entries under the 40 CFR 180.1002 exemption.]

Conclusions:

No acceptable data were submitted pertaining to residues of allethrin in or on any plant commodity following registered preharvest applications. The following data are required:

- Data depicting allethrin residues of concern in or on (i) greenhouse and field grown snap beans, dry beans and bean vines (field-grown only), broccoli, cabbage, collards, lettuce (leaf and head - with and without wrapper leaves), radishes, and tomatoes harvested immediatly after the last of multiple foliar treatments of the 2.5% EC formulation at 36 fl. oz. product/100 gal water/A; (ii) apples, oranges and peaches harvested immediatly after the last of multiple foliar treatments of the 1% EC formulation at 1 quart product/A using both high and low (2 gal/A) volume ground equipment in separate tests; (iii) celery and horseradish harvested immediatly after the last of multiple foliar treatments of the 1% EC formulation at 1.5 pints product/A in 1 gal water/A; and, to support a FL 24(c) label (FL780061), (iv) alfalfa forage and hay, cucumbers, melons, summer squash, potatoes, grain sorghum (grain, forage, fodder, silage and hay), sweet sorghum (seed, forage and fodder), and sugarcane (cane and forage) harvested one day after multiple foliar applications, made at 5-day intervals, of the 0.9% EC formulation at 2 pints product/A in 1 gal water/A. A maximum number of applications per season must be proposed for all uses and reflected in the submitted data. Tests must be conducted in states that represent the major growing regions for each crop according to the latest edition of Agricultural Statistics (USDA) or the Census of Agriculture (U.S. Dept. of Commerce), except to support the FL 24(c) label (tests need be conducted in FL only). Appropriate tolerances must be proposed.

- Data depicting allethrin residues of concern in the following processed commodities obtained from raw agricultural commodities bearing measurable weathered residues: wet and dry pomace and juice from apples; dried pulp, oil, molasses, and juice from oranges; flour, starch and grain dust from grain sorghum; syrup from sweet sorghum; molasses, refined sugar, and bagasse from sugarcane; and wet and dry pomace, puree, catsup, and juice from tomatoes. If residues concentrate, appropriate food/feed additive tolerances must be proposed.

- The Registrant(s) must propose a preharvest use on Jerusalem artichokes, sugar beets, carrots, chicory, corn (sweet and field), garlic, leeks, onions, parsnips, salsify, shallots, and sweet potatoes accompanied by appropriate residue data (currently, an entry exists in 40 CFR 180.1002 for these commodities but no registered uses on them exist). Processing studies must be submitted for field corn (crude and refined oil, grain dust, and milling products [starch, grits, meal, flour]), and sugar beets (dehydrated pulp, molasses and refined sugar). If the rate proposed (i) on Jerusalem artichokes and sweet potatoes is no higher than that registered for use on potatoes; and (ii) on sugar beets, parsnips, salsify and carrots no higher than on radishes, no residue data for these crops need be submitted (processing data would still be required). Also, if the uses

proposed on garlic, leeks, onions and shallots are identical, data need be submitted only for onions (green and bulb). Appropriate tolerances must be proposed.

Upon receipt of the requested data, the current exemptions from the requirement of tolerances will be revoked and replaced by individual tolerances to cover residues following preharvest use, if toxicological considerations permit.

There are no Canadian or Mexican tolerances or Codex MRLs for residues of allethrin in or on any plant commodity; therefore, no compatibility question exists with respect to Codex.

References (used):

MRID: 00089616.

Discussion of the data.

Niagra Chemical (1954; MRID 00089616) submitted information pertaining to calculated residues of allethrin in or on cabbage, snap beans, sweet corn, spinach, tomatoes, and mushrooms. These calculated data, based on yield per acre (lbs), lb product applied per acre, and percentage of edible commodity portion, are not acceptable for purposes of tolerance evaluation.

Mushrooms

Tolerance:

Allethrin (allyl homolog of cinerin I) is exempted from the requirement of a tolerance for residues when used before harvest in the production of mushrooms (40 CFR 180.1002).

Use directions and limitations:

The 2.5%-12.51% SC/L-MAI and the 1.25% RTU-MAI formulations (004001) are registered for use as a premise treatment in mushroom houses at 1 fl. oz of formulation/1,000 cu ft (0.1-0.25% finished spray for the SC/L and 1.25% finished spray for the RTU). Applications are to be made using mechanical fogging equipment. No maximum number of applications has been established. No PHI is in effect.

Conclusions:

No data have been submitted pertaining to residues of allethrin in or on mushrooms. The following are required:

- Data depicting allethrin residues of concern in or on mushrooms grown in mushroom houses in which multiple premise treatments have been made with the 1.25% RTU as a 1.25% finished spray. A maximum number of applications must be proposed and supporting data submitted. An appropriate tolerance must be proposed.

Upon receipt of the requested data, the current exemption from the requirement of a tolerance for residues in or on mushrooms will be revoked and replaced by a tolerance, if toxicological considerations permit.

No Canadian or Mexican tolerance or Codex MRL has been established for residues of allethrin in or on mushrooms; therefore, no compatibility question exists with respect to Codex.

References (used):

N/A.

Discussion of the data:

N/A.

Food/Feed Commodities with Established Tolerances for Residues

Fruits and Vegetables

Tolerances:

Tolerances of 4 ppm have been established for residues of allethrin (allyl homolog of cinerin I) as a result of a postharvest treatment in or on the following crops: apples, blackberries, blueberries (huckleberries), boysenberries, cherries, crabapples, currants, dewberries, figs, gooseberries, grapes, guavas, loganberries, mangoes, muskmelons, oranges, peaches, pears, pineapples, plums (fresh plums), raspberries, and tomatoes (40 CFR 180.113).

Use directions and limitations:

The 2.5% EC-MAI formulation (004001) is registered for postharvest use as a 0.012% emulsion dip or 4 pt formulation/100 gal water. The application may be made in storage, processing plants, or in the field at the time of harvest on: apples, blackberries, blueberries, boysenberries, cherries, crabapple, currants, dewberries, grapes, muskmelons, oranges, peaches, pears, pineapples, plums, and raspberries.

Conclusions:

No data were submitted pertaining to postharvest residues of allethrin in or on fruits and vegetables. The following data are required:

- Data depicting allethrin residues of concern in or on apples, blackberries, plums, blueberries, grapes, muskmelons, oranges, peaches, and pineapples. Samples must be taken (in separate tests) immediately following a 0.012% emulsion dip treatment with the 2.5% EC formulation.

- Data depicting allethrin residues of concern in the following processed commodities obtained from postharvest-treated raw agricultural commodities: raisins, wet and dry pomace, raisin

waste and juice from grapes; raisin and juice from pineapples; and dried prunes from plums. If residues concentrate in these processed commodities, appropriate food/feed additive tolerances must be proposed.

- The Registrant(s) must propose a postharvest use on figs, gooseberries, guavas, loganberries, mangoes, and tomatoes accompanied by residue data in support of the established tolerances for residues in or on these commodities. Processing data must be submitted for figs (dried figs). If the rate proposed on gooseberries and loganberries is no higher than that registered for use on blueberries and blackberries, then no residue data for gooseberries or loganberries need be submitted. If these data and/or proposed uses are not submitted, the tolerances for allethrin residues in/on the crops will be revoked.

There are no Canadian or Mexican tolerances or Codex MRLs for residues of allethrin in or on any plant commodity; therefore, no compatibility question exists with respect to Codex.

References (used):

N/A.

Discussion of the data:

N/A.

MAGNITUDE OF THE RESIDUE IN STORED RAW AGRICULTURAL COMMODITIES

Tolerances:

Tolerances of 2 ppm have been established for residues of allethrin (allyl homolog of cinerin I) following postharvest treatment, in or on barley, corn, grain sorghum, milo, oats, rye, and wheat grains (40 CFR 180.113).

Use directions and limitations

Cereal grains (barley, corn, oats, rye, sorghum, wheat): The 2.5-15% EC-MAI, the 5-12.51% SC/L-MAI, and the 0.25% RTU-MAI formulations (004001) are registered for use on barley, corn, oats, rye, sorghum, and wheat as a stored commodity treatment. Applications may be made at 5 gal/1,000 bu or 1 gal/1,000 sq ft of grain (0.1-0.5% finished spray) as the grain goes into storage at such a point that the grain will be tumbled and mixed before entering the storage bin. Small lots of grain may be sprayed and mixed by hand. For certain insect pests, applications may be made to the surface of binned grain at 30-day intervals until early fall. The 15% EC-MAI formulation (004001) is registered for surface spray to grain storage bins prior to grain storage at 1 gal/750 sq ft (0.25-0.5% finished spray). Ceilings, walls, partition boards, and all cracks and crevices are to be thoroughly wetted after the bin has been cleaned.

Dried fruit: The 5% SC/L-MAI formulation (004001) is registered for application as a fine mist above shelves and trays of dried fruit processing and storage areas at 1 fl. oz/1,000 cu ft Treatments may be repeated at 30-day intervals. The 0.326% RTU-MAI formulation (004004) and the 0.5% RTU-MAI formulation (004003) are registered for application as a fine mist as needed above trays or shelves of dried fruit at 1 gal/50,000 cu ft. Overhead sprays should be discharged at least 6 ft above top trays of fruit and not applied to fruit directly.

Stored food: The 5% SC/L-MAI and 0.25% RTU-MAI formulations (004001) are registered for stored commodity treatment as a space spray at 1 fl. oz/1,000 cu ft (5% finished spray) and 0.25% finished spray, respectively. Applications may be made as needed to storage areas of stored food (multiwalled or cloth bags). The 0.326% RTU-MAI formulation (004004) in also registered for use as a stored commodity (stored in multiwall paper bags or in cloth bags) space spray treatment at 1 fl. oz/1,000 cu ft. The 0.5% RTU-MAI formulation (004003) is registered for space spray treatments as necessary at 1 fl. oz/1,000 cu ft dispensed as a fine mist through conventional or fixed ceiling sprayers.

Conclusions:

No data were submitted pertaining to postharvest residues of allethrin in or on stored raw agricultural commodities. The following data are required:

- Data depicting allethrin residues of concern in or on corn and wheat treated with an EC, SC/L, and RTU formulation in separate tests at 5 gal/1,000 bu (0.5% finished spray) in such a way that the grain will be tumbled and mixed before it enters the storage bin. The surface

of the binned grain must also be treated with the same formulations (in separate tests) at 1 gal/1,000 sq ft of grain (0.5% finished spray every 30 days from the time of storage until early fall). The storage bin must have a surface application of the 15% EC at 1 gal/750 sq ft just prior to the storage of the grain. Samples must be collected on the day they enter the storage bin and on the day of the last surface treatment in early fall.

- Data depicting allethrin residues of concern in grain dust and milled products of field corn and wheat (including the wet milled products of corn - starch, crude oil and refined oils, the dry milled products of corn - grits, meal, flour, crude and refined oils; and bran, flour, middlings and shorts for wheat). Samples must be processed from grains bearing measurable weathered residues from postharvest treatments. If concentration occurs, appropriate food/feed additive tolerances must be proposed.

- Data depicting allethrin residues of concern in or on dried fruit (dried apples, prunes, raisins, bananas, figs, dates) sampled immediately following treatment with a 5% SC/L at 1 fl. oz/1,000 cu ft and a 0.326% RTU at 1 gal/50,000 cu ft (in separate tests). These formulations are to be discharged as a fine mist above dried fruit. The registrant(s) must propose an appropriate tolerance for allethrin residues in stored dried fruit.

- Data depicting allethrin residues of concern in representative raw agricultural commodities (dried beans, cocoa beans, coffee beans, corn, nuts, peanuts, and soybeans) collected immediately following an indoor space spray with the 5% SC/L and a RTU formulation at 1 fl. oz/1,000 cu ft. The registrant(s) must propose an appropriate tolerance for allethrin residues in stored raw agricultural commodities.

There are no Canadian or Mexican tolerances or Codex MRLs for residues of allethrin in stored raw agricultural commodities; therefore, no compatibility question exists with respect to Codex.

References (used):

N/A.

Discussion of the data:

N/A.

MAGNITUDE OF THE RESIDUE IN MEAT, MILK, POULTRY AND EGGS

Tolerances:

Presently, no tolerance exists for residues of allethrin in any animal commodity.

Use directions and limitations:

Allethrin (004001) formulations registered for premise treatment use in farm animal quarters include: (i) the 2.5-3.42% EC-MAI formulations in a 0.25-0.5% finished spray and the 0.25-1.25% RTU-MAI as a surface spot, crack and crevice treatment to be repeated as needed; (ii) the 1% EC formulation as a 0.17% finished spray, and the 1.875% EC-MAI, 2-12.51% SC/L-MAI, the 0.25% RTU-MAI, and the 0.6% PrL-MAI formulations as an 0.08-0.6% finished space spray applied using a fogger or a mist generator; and (iii) the 1% EC formulation as a 0.17% finished spray as an automatic indoor space spray or applied with ultra low volume equipment. Space sprays must be directed to the center of the animal quarters and distributed as evenly as possible. Additionally, the 0.066% SC/L-MAI is registered for surface spray use in poultry houses in a 0.33% finished spray to be repeated as needed.

Bioallethrin (004003) is registered for use in farm milk houses as an 0.8% PrL-MAI (0.8% finished spray) to be applied through an automatically-timed discharging device. A dosage of 27.5 mg may be discharged every 7.5 minutes.

Allethrin (004001) formulations registered for direct treatment to horses and ponies include: (i) the 1-1.875% EC-MAI and 5-12.51% SC/L-MAI in a 0.1-0.5% finished spray; and (ii) the 0.25-1.25% RTU-MAI in a 0.25-1.25% finished spray. Applications may be made to the legs, shoulders, shanks, neck, and facial areas as a wipe (skin should not be wetted) or to stable area and stabled horses as a spray; treatments may be repeated daily or as required. The 1.875% EC-MAI (004001) may be applied as needed to horses and ponies as a 0.03% finished spray to thoroughly wet the skin..

Conclusions:

Presently, the nature of the residue in plants animals is not adequately understood. In addition, numerous data gaps exist concerning the magnitude of the residue in feed items of animals. Therefore, the expected dietary intakes for dairy cattle, beef cattle, swine, and poultry will not be calculated. Upon receipt of data requested in the section entitled "Nature of the Residue in Animals" and that requested for feed commodities, the need for and nature of tolerances for residues in animal products will be determined. Data requirements regarding the magnitude of the residues in animal products will not be determined until all requested data regarding metabolism in animals and magnitude of residues in feed items have been received.

No Canadian or Mexican tolerance or Codex MRL has been established for residues of allethrin in animal commodities. Therefore, no questions of compatibility exist.

References (used):

MRID: 00135387.

Discussion of the data:

The residue data presented below were obtained using a qualitative colorimetric method considered inadequate for data collection; the data are included here for informational purposes only. FMC Corp. (1956; MRID 00135387) submitted a study in which three cows were sprayed with an unspecified formulation of bioallethrin daily for 3 weeks at a concentration of 1%, 20%, or 10%, finished spray (one cow/concentration) for a total amount of 1.5 oz finished spray/cow/day. Milk samples were collected three times/week for 3 weeks. In a separate test, an 80 lb female goat received a daily spray for 5 weeks with an unspecified formulation containing 20% bioallethrin at 1.5 oz/day.

The goat was sacrificed at the end of the treatment period and samples of the flank, rump, loin, liver, heart, kidney, and tallow were immediately frozen. Milk from the dairy cows and goat tissue samples were subjected to qualitative analysis using a colorimetric method; negative color development (i.e., absence of bioallethrin) was reported for all milk and tissue samples tested except for tallow [fat] samples, which gave excessive interferences.

NATURE AND MAGNITUDE OF THE RESIDUE IN FOOD HANDLING ESTABLISHMENTS

Tolerances:

No tolerances or regulations have been established covering residues of allethrin in or on foods resulting from treatment of food handling establishments.

Use directions and limitations:

The allethrin (004001), bioallethrin (004003), and d-trans allethrin (004004) formulations (all formulated with other active ingredients) registered for contact crack and crevice and/or space spray treatments in food handling establishments are presented in Table 2.

Table 2. Food Handling Establishment uses.

Shaughnessy No.	Treatment	Formulation and rate	Use pattern[a]
004001	contact spray	2.5% EC, 2.5-12.51% SC/L, and 0.25-1.25% RTU as a 0.2-2.5% finished spray; 0.1-0.1625 PrL as a 0.1-0.16% finished spray.	Apply as a coarse, wet spray into cracks and crevices in shelves, pantries, and food storage areas.
004001	space spray	2.5-12.51% SC/L as a 0.1-0.25% finished spray; 2.5% EC, 0.3-1.25% RTU, and 0.5-0.6% PrL as a 0.3-1.25% finished spray; and 0.066% SC/L as a 0.033% finished spray.	Apply using a fogger or mist generator. Treated area should be closed for at least 10 min before ventilation.
004001	space and contact sprays	2.5-12.51% SC/L, 1.25% RTU as a 1.25-12.51% finished spray.	Direct contact spray into cracks and crevices, and space spray towards ceiling. Close area for 1 hr. Repeat as needed.
004003	contact spray	0.837-6% EC and 0.05-0.6% RTU as a 0.05-0.6% finished spray; and 0.05-0.5% PrL as a 0.05-0.5% finished spray.	Apply as a spot, crack and crevice treatment, as needed.
004003	contact spray	0.05-0.1% RTU as a 0.05-0.1% finished spray.	Apply as needed into cracks and crevices using equipment capable of delivering a pin stream.

Table continued.

Table 2. (Continued).

Shaughnessy No.	Treatment	Formulation and rate	Use pattern[a]
004003	space spray	0.1-0.5% PrL as a 0.1-0.5% finished spray; 6% EC and 0.075-0.6% RTU as a 0.075-0.6% finished spray or thermal dry fog; 0.1% RTU as a 0.1% finished spray.	Apply with mechanical or compressed air sprayer or fogger adjusted for small particle size. Direct spray to all parts of the room. Close room for 15 min.
004003	space spray	0.9% PrL as a 0.9% finished spray.	Dispense in an automatic activator at 100 g/15 min/6,000 cu ft of space for 12 hr. The dispensing unit is not to be installed directly over a food handling or dispensing area and is to be operated only "after hours".
004003	space spray	0.8% PrL as a 0.8% finished spray.	Dispense through an automatic activator at 55 mg/15 min/6,000 cu ft of space.
004004	space and contact sprays	0.116-0.186% PrL.	Apply as a contact, surface, or space spray (5-10 sec/1,000 cu ft) as needed. Food should be removed or covered during treatment and all food processing surfaces should be covered during treatment or thoroughly cleaned prior to using.
004004	crack and crevice	0.788% EC in a 1:16 dilution; and 0.036% RTU at 1 fl. oz/1,000 sq ft	Apply as needed into cracks and crevices using equipment capable of delivering a pin stream.
004004	crack and crevice	0.326% RTU at 1 gal/1,000 sq ft.	Apply as a coarse wet spray.

footnote on next page

a 004001 and 004003: Do not apply as a space spray while food processing is underway. Surface sprays may be made during processing operations except in federally inspected meat and poultry plants. Foods should be removed or covered before treatments and food processing surfaces should be washed before reuse. If washing of equipment and food processing surfaces prior to reuse is impractical, do not allow food to come in contact will treated surfaces for at least 48 hours; 004004: Avoid contamination of food or food processing surfaces.

Conclusions:

The magnitude of bioallethrin residues in food products resulting from food handling establishment uses has not been adequately elucidated. The following additional data are required:

- Data depicting residues of concern in food products resulting from applications of allethrin in food service, food manufacturing, and food processing establishments (two representative types of each food handling establishment as listed in Table 1 of Subdivision O [Residue Chemistry] of the Pesticide Assessment Guidelines). Tests are required in these establishments utilizing an SC/L and RTU formulation as a general contact spray and space spray (in separate tests) in 12.5% ai finished spray. Tests conducted must be representative examples of worst-case scenarios for potential residue contamination of food products which include the following: (i) particulate aerosol contact with packaged products or unwrapped fresh produce present at the time of treatment; (ii) contact of packaged foods with treated surfaces, such as flour sacks stacked on treated floor surfaces in storage areas; (iii) accidental treatment of food work surfaces and subsequent contact of food before surfaces are cleaned; (iv) treatment occurring near stacks of new or cleaned product containers that are filled without being cleaned; and (v) tracking of residues by insects or rodents from treated areas to food or food contact surfaces. Exposure situations in grocery stores and restaurants must include a representative range of foods such as oily foods, baked cereal products, raw and cooked meats, and fresh fruits and vegetables.

- The registrant(s) must propose a tolerance for residues of bioallethrin in food/feed exposed during or following treatment of food/feed handling establishments.

References (used):

MRIDs: 00031925. 00031927. 00031928. 00031930. 00063081. 00064646.

References (not used):

[The following reference does not contain data relevant to the magnitude of the residues in food handling establishments.]

MRID: 00031929.

Discussion of the data:

McLaughlin Gormley King Co. (1979; MRID 00031927, and 19??; MRIDs 00031930 and 00031925) submitted a study pertaining to allethrin (004003) residues in foods resulting from space spray and contact spray treatments with a 0.6% ai formulation. The space spray treatments consisted of a single upward spray at 0.5 fl. oz/1,000 cu ft in the morning and at 2.5 fl. oz/1,000 cu ft in the afternoon of the same day in an unventilated 8,640 cu ft room in the presence of three samples each of representative foods (one packaged, one packaged and covered, and one exposed). The room was sealed for 30 min. following each treatment and then ventilated before samples were removed. The same types of foods were present in an 832 cu ft room which was treated with a coarse, wet contact spray. Food samples from spray and contact treatments were frozen for an unspecified interval prior to analysis using an adequate GLC/EC method. Allethrin residues were nondetectable (<0.1 ppm) in one sample each of packaged/covered, packaged/ uncovered, and unpackage/uncovered candy, butter, potato, lemon cream pie, meat, and bread following contact spray exposure. Allethrin residues in foods following space spray exposure are detailed in Table 3 on page 22.

Recoveries following fortification at 0.1-0.3 ppm were 83-100% for candy, 73-80% for butter, 90-110% for potato, 87-93% for lemon cream pie, 70-99% for meat, and 63-90% for bread. Residues were <0.1 ppm (nondetectable) in control samples of all tested foods.

McLaughlin Gormley King Co. (1980; MRID 0031928, and 19??; MRID 00031930) submitted a study pertaining to allethrin residues in bread resulting from space spray treatments with unspecified 0.6% (004005), 0.375% (004003), 1% (004001), and 0.4% (004004) allethrin formulations at 0.5 and 2.5 fl. oz/1,000 cu ft. A fine oscillating spray was directed upwards from two locations in a 1,000 cu ft room in the presence of one loaf of bread in its original cellophane tie-bag and covered with two pieces of waxed paper;

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Table 3. Bioallethrin (004003) residues in food following space spray exposure at two application rates.

	Bioallethrin residues (ppm)					
	0.5 fl oz/1,000 cu ft			2.5 fl oz/1,000 cu ft		
Food	P(C)[a]	P(UC)[b]	UP[c]	P(C)	P(UC)	UP
Candy	<0.1	<0.1	0.24	<0.1	<0.1	1.65
Butter	0.11	0.12	0.23	1.3	1.5	1.67
Potato	<0.1	<0.1	0.13	<0.1	<0.1	1.02
Lemon cream pie	<0.1	<0.1	0.23	<0.1	<0.1	0.75
Meat	<0.1	<0.1	0.18	<0.1	0.29	1.68
Bread	<0.1	<0.1	1.97	0.22	0.18	11.5

[a]P(C) = packaged and covered
[b]P(UC) = packaged and uncovered
[c]UP = unpackaged and uncovered

one loaf of bread in its original wrapper, uncovered; and individual exposed slices of bread (one loaf). Thirty minutes after exposure the room was ventilated and the samples were removed. Tests with all formulations at both rates were conducted on the same day; details regarding intervals between treatments or sequence of treatments were not provided. Bread samples were frozen for an unspecified interval prior to analysis using an adequate GLC/EC method. Recoveries following fortification at 0.2 ppm were 80% for allethrin (004001), 95% for d-cis/trans allethrin (004005), 105% for S-bioallethrin (004004), and 85% for bioallethrin (004003). Residues of the various bioallethrin compounds in bread are presented in Table 4.

Table 4. Residues of allethrin (004001), bioallethrin (004003), S-bioallethrin (004004), and d-cis/trans allethrin (004005) in bread following space spray exposure at two application rates[a].

	Compound							
	004001		004003		004004		004005	
Exposure	0.5	2.5	0.5	2.5	0.5	2.5	0.5	2.5
Packaged/covered	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Packaged/uncovered	<0.1	<0.1	0.22	0.13	<0.1	0.32	0.17	0.16
Unpackaged/uncovered	5.39	24.7	1.84	7.78	1.83	9.30	2.0	14.7

[a] 0.5 and 2.5 fl. oz/1,000 cu ft.

McLaughlin Gormley King Co. (1978; MRIDs 00063081 and 00064646) submitted a study pertaining to allethrin residues in food resulting from a space spray treatment with an unspecified PrL-MAI formulation containing 0.35% d-cis/trans allethrin (004005). Treatment consisted of an upward spray for 90-105 seconds in an unventilated room (8,640 cu ft) at 8.19-10.92 g

product/1,000 cu ft in the presence of two samples each (one covered with a paper towel and the other exosed) of apples, butter, hamburger meat, sugar, white bread, and white potatoes. This treatment regimen was repeated three times on the same day in the same room. Thirty minutes following treatment, the room was ventilated and the food samples were collected and stored at -20 C for an unspecified interval prior to residue analysis using an adequate GLC/EC method. Recoveries for d-cis/trans allethrin (004005) following fortifiation at 0.1-0.6 ppm were 85-100% for sugar, 57-92% for butter, 80-97% for potato, 84-100% for apple, 72-92% for bread, and 75-83% for meat. Residues in control samples of each tested food were nondetectable (<0.1 ppm). Data were reported from three replicate samples of each food. Residues of d-cis/trans allethrin in covered samples of all foods tested, and uncovered samples of butter, potato, and apple were nondetectable (<0.1 ppm); uncovered samples of sugar, bread, and meat contained residues of <0.1 (nondetectable)-0.25 ppm, 0.1-0.21 ppm, and <0.1 (nondetectable)-0.13 ppm, respectively.

MAGNITUDE OF THE RESIDUE IN FOOD RESULTING FROM INDOOR DOMESTIC DWELLING USES

Tolerance:

No tolerance has been established for allethrin residues in food resulting from indoor domestic dwelling uses.

Use directions and limitations:

The 2.5-5% SC/L-MAI and 0.25% RTU-MAI allethrin formulations (004001) are registered for contact crack and crevice and upward-directed space spray treatments as needed at 0.5-1 fl. oz/1,000 cu ft using a mechnical aerosol generator or fogger. The treated area is to be closed for 1 hour. The 0.6% PrL-MAI formulation (004001) is also registered for contact crack and crevice and space spray treatments as needed as a 0.6% finished spray.

The following d-cis/trans allethrin (004005) formulations are registered for use as contact spray treatments: 0.31% SC/L-MAI at 0.5 fl. oz formulation/1,000 cu ft; and 0.129, 0.19, 0.239, 0.422, 0.48, 0.5% PrL-MAI at unspecified rates. Treatments are to be made into cracks and crevices. Foods should be covered and all food processing surfaces and utensils should be covered during treatment or thoroughly washed before use.

The following S-bioallethrin (004004) formulations are registered for contact and/or space spray treatments as needed: 2.973% EC-MAI; 0.928 and 1.394% SC/L-MAI; 0.163-0.372 and 0.0232-0.0603% RTU-MAI; and 0.116-0.197 and 0.025-0.0[illegible] PrL-MAI. Contact and surface spray applications with EC, SC/L, and some RTU formulations may be made at 1 gal/1,000 sq ft; the PrL formulation is applied at 1-2 ft/sec. Space spray treatments with EC, SC/L, and RTU formulations are applied diluted at 0.5-1 fl. oz/1,000 cu feet or undiluted at 0.5 fl oz/1,000 cu ft using a mechanical or compressed air sprayer or fogger. Treatments may be made as needed. All food processing surfaces and utensils should be covered during treatment or thoroughly washed prior to use. Exposed food should be covered or removed.

Conclusions:

No data were submitted to support the homeowner uses registered for bioallethrin which may result in residues of concern in food. Since private residences are exempted from regulation as food handling establishments (FR 73-16536; 8-9-73), no additional information is required for this topic.

References (used):

N/A.

Discussion of the data:

N/A.

REGULATORY INCIDENTS

FDA monitoring data are available pertaining to allethrin residues in or on food commodities tested through domestic and import surveys over the period FY 1978-1987 (FDA printout dated 3/20/87; data received through 3/9/87) using methodology known to be capable of determining allethrin. Allethrin residues were determined using extraction procedures in PAM I 212.1, 211.1, 232.4, or 242.1 and detection with GLC/EC or GLC/FPD. No findings of allethrin were reported in the revised Total Diet Study samples (all 234 food items) collected in April 1982-April 1986. Allethrin residues were not detected in or on any crop for which there is an established tolerance or exemption from the requirement of a tolerance for allethrin residues. A single import sample of cumin seed collected in 1986 bore allethrin residues of 0.02 ppm; no other cumin samples were analyzed.

TOLERANCE REASSESSMENT

The meager available data are insufficient to evaluate the adequacy of the established tolerances (covering postharvest use) for residues of allethrin (allyl homolog of cinerin I) in or on the food/feed items listed in 40 CFR 180.113. The available data are also insufficient regarding the magnitude of residues in/on a variety of food and feed crops following registered preharvest use or treatment of food handling establishments. In addition, plant and animal metabolism data, storage stability data, and residue data depicting residues in meat, milk, poultry, and eggs following direct treatment and/or ingestion of residues are required.

Due to the potential for cumulative residues occurring in/on food items as a result of preharvest and postharvest treatments, and use of allethrins in food handling establishments, it is important that, on receipt of all required residue data, the residue situation for each commodity be assessed such that all avenues of potential exposure of the commodity to allethrins are considered.

To avoid unnecessary expense and repetition of residue tests (field trials, processing studies, postharvest use trials, and food handling establishment use tests), RCB recommends that the required plant metabolism data be submitted for review prior to initiation of residue trials.

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MASTER RECORD IDENTIFICATION NUMBERS

[The following references were selected from the Master Record Sequence Bibliography for bioallethrin dated 9/10/86.]

References (used):

00031925. McLaughlin, Gormley, King Co. 19??. Residue study--Allethrin space and contact sprays--simulated food processing situations. (Unpublished study received Apr. 23, 1980 under 1021-1471; CDL:242342-A.)

00031927. McLaughlin, Gormley, King Co. 1979. Primary Space Spray Test. (Unpublished study received Apr. 23, 1980 under 1021-1471; CDL:242342-C.)

00031928. McLaughlin, Gormley, King Co. 1980. Linking Space Spray Test: Other Allethrins. (Unpublished study received Apr. 23, 1980 under 1021-1417; CDL:242342-D.)

00031930. McLaughlin, Gormley, King Co. 19??. Residue analysis of d-trans allethrin, MGK-264, and Piperonyl Butoxide in candy, butter, potatoes, lemon cream pie, bread and meat. Undated method. (Unpublished study received Apr. 23, 1980 under 1021-1417; CDL:242342-F.)

00035929. Schreiber, A.A.; McClellan, D.B. 1954. Estimation of micro quantities of Pyrethroids. Analytical chemistry 26(3):604-607. (Also in unpublished submission received Oct. 14, 1955 under PP0044; submitted by FMC Corp.; CDL:092325-G.)

00063081. McLaughlin Gormley King Co. 1978. Residues of Neo-pynamin, Sumithrin and Pynamin Forte Resulting from Use of a Water-base Pressurized Space Spray. (Unpublished study received Oct. 29, 1980 under 1H5283; CDL:243803-H.)

00064646. Meinen, V.J.; Carlson, D.J. 19??. Residue analysis of Sumithrin-Neo-pynamin- and Pynamin Forte- in sugar, butter, potatoes, apples, bread and meat. Undated method. (Unpublished study received Oct. 29, 1980 under 1H5283; submitted by McLaughlin, Gormley, King Co.; CDL:243803-I.)

00089450. Weevil-Cide Co. 1955. Remaining residues of Allethrin in and on grain. (Unpublished study received July 6, 1957 under PP0142; CDL:090170-B.)

00089616. Niagara Chemical. 1954. Remaining residues of allethrin on fresh vegetables. (Unpublished study, including published data, received on unknown date under PP0020; CDL:090019-F.)

00135387. FMC Corp. 1956. Residue studies of Allethrin in guernsey milk and goat meat and fat. (Compilation; unpublished study received 1956 under PP0044-A; CDL:098144-A.)

Zee, King. 1980. FAP#0H5265. Results of method trial for allethrin in food handling establishments. (No MRID assigned).

7/ Data must be submitted no later than 7 months after the publication of this Standard.
8/ A 90-day dermal study is not required for this use pattern.
9/ This requirement is reserved pending the receipt and review of the Exposure Assessment for this chemical.
10/ This study is not required because the acute toxicity study in the hen is not required. Occasionally, in this class of chemicals, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals if appropriate preservation and staining techniques are employed.
11/ Data must be submitted no later than 42 months after the publication of this Standard.
12/ Data must be submitted no later than 42 months after the publication of this Standard.
13/ Data must be submitted no later than 42 months after the publication of this Standard.
14/ Data must be submitted no later than 42 months after the publication of this Standard.
15/ Data must be submitted no later than 12 months after the publication of this Standard.
16/ Data must be submitted no later than 12 months after the publication of this Standard.
17/ Data must be submitted no later than 20 months after the publication of this Standard.
18/ Data must be submitted no later than 10 months after the publication of this Standard.
19/ Data must be submitted no later than 10 months after the publication of this Standard.
20/ Data must be submitted no later than 10 months after the publication of this Standard.
21/ Data must be submitted no later than 14 months after the publication of this Standard.

F. Toxicology Summary Tables (Continued)

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING ALLETHRIN

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING:				
81-1 - Acute Oral - Rat	MP	No	-	Yes
81-2 - Acute Dermal	MP	No	-	Yes
81-3 - Acute Inhalation - Rat	MP	No	-	Yes
81-4 - Eye Irritation - Rabbit	MP	No	-	Yes
81-5 - Dermal Irritation - Rabbit	MP	No	-	Yes
81-6 - Dermal Sensitization - Guinea Pig	MP	No	-	Yes

1/ Composition: MP= Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.

F. Tox. -ogy Summary Tables

TABLE A

GENERIC DATA REQUIREMENTS FOR D-CIS/TRANS ALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	B,F,H,I	No	---	Yes
81-2 - Acute Dermal	TGAI	B,F,H,I	No	---	Yes
81-3 - Acute Inhalation - Rat	TGAI	B,F,H,I	No	---	Yes
81-4 - Eye Irritation - Rabbit	TGAI	B,F,H,I	No	---	Yes
81-5 - Dermal Irritation - Rabbit	TGAI	B,F,H,I	No	---	Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI	B,F,H,I	No	---	No 4/
81-7 - Acute Delayed Neurotoxicity - H n					
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					No 5/
Rodent	TGAI	B,F,H,I	No	---	Yes 6/
Non-rodent	TGAI	B,F,H,I	No		

TABLE A
GENERIC DATA REQUIREMENTS FOR D-CIS/TRANS ALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal -	TGAI	B,F,H,I	No	---	Yes 7/
82-3 - 90-Day Dermal -	TGAI	B,F,H,I	No	---	No 8/
82-4 - 90-Day Inhalation -	TGAI	[Reserved] 9/	No	---	[Reserved] 9/
82-5 - 90-Day Neurotoxicity -	TGAI	B,F,H,I	No	---	No 10/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	B,F,H,I	Yes	---	No
Non-rodent	TGAI	B,F,H,I	No	---	Yes 11/
83-2 - Oncogenicity Study -					
Rat	TGAI	B,F,H,I	Yes	---	No
Mouse	TGAI	B,F,H,I	No	---	Yes 12/
83-3 - Teratogenicity -					
Rat	TGAI	B,F,H,I	No	---	Yes 13/
Rabbit	TGAI	B,F,H,I	No	---	Yes 14/
83-4 - Reproduction -	TGAI	B,F,H,I	No	---	Yes 15/

TABLE A
GENERIC DATA REQUIREMENTS FOR D-CIS/TRANS ALLETHRIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	B,F,H,I	No	---	Yes 16/
84-2 - Chromosomal Aberration	TGAI	B,F,H,I	No	---	Yes 17/
84-2 - Other Mechanisms of Mutagenicity	TGAI	B,F,H,I	No	---	Yes 18/
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B,F,H,I	No	---	Yes 19/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by case basis.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C= Aquatic, Food Crop; D = Aquatic, Non-Food; E= Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.
3/ Unless otherwise specified, data must be submitted no later than six months after publication of this Standard.
4/ This study is not required since the test article is not an organophosphate.
5/ Subchronic feeding data on Technical d-cis/trans Allethrin need not be submitted because chronic studies on Technical d-cis/trans Allethrin in the rat have been submitted. However, the Registrant should be aware that subchronic studies are useful and often necessary in determining the maximum tolerated dose (MTD) used for oncogenicity studies in rodents (mice and rats). If data are to be submitted, it must be submitted no later than 12 months after publication of this Standard.
6/ Subchronic feeding data on Technical d-cis/trans Allethrin in a nonrodent species need not be submitted if a chronic study on Technical Allethrin in a nonrodent species is submitted. If subchronic data are to be submitted, it must be submitted no later than 12 months after the publication of this Standard.

7/ Data must be submitted no later than 7 months after the publication of this Standard.
8/ A 90-day dermal study is not required for this use pattern.
9/ This requirement is reserved pending the receipt and review of the Exposure Assessment for this chemical.
10/ This study is not required because the acute toxicity study in the hen is not required. Occasionally, in this class of chemicals, neurotoxic effects have been observed in mammals in long-term studies. Any expected neurotoxic effects related to exposure to this chemical should show up in the subchronic and chronic studies in mammals if appropriate preservation and staining techniques are employed.
11/ Data must be submitted no later than 42 months after the publication of this Standard.
12/ Data must be submitted no later than 42 months after the publication of this Standard.
13/ Data must be submitted no later than 12 months after the publication of this Standard.
14/ Data must be submitted no later than 12 months after the publication of this Standard.
15/ Data must be submitted no later than 20 months after the publication of this Standard.
16/ Data must be submitted no later than 10 months after the publication of this Standard.
17/ Data must be submitted no later than 10 months after the publication of this Standard.
18/ Data must be submitted no later than 10 months after the publication of this Standard.
19/ Data must be submitted no later than 14 months after the publication of this Standard.

F. Toxi .ogy Summary Tables (Continued)

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING D-CIS/TRANS ALLETHRIN

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING:				
81-1 - Acute Oral - Rat	MP	No	-	Yes
81-2 - Acute Dermal	MP	No	-	Yes
81-3 - Acute Inhalation - Rat	MP	No	-	Yes
81-4 - Eye Irritation - Rabbit	MP	No	-	Yes
81-5 - Dermal Irritation - Rabbit	MP	No	-	Yes
81-6 - Dermal Sensitization - Guinea Pig	MP	No	-	Yes

1/ Composition: MP= Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard.

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

MAY 15 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Bioallethrin Registration Standard

FROM: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

TO: Amy Rispin
Science Integration Staff
Hazard Evaluation Division (TS-769C)

and

Arturo Castillo (PM 17)
Insecticide/Rodenticide Branch
Registration Division (TS-767C)

Attached are the Product and Residue Chemistry Chapters for the Bioallethrin Registration Standard prepared by Dynamac Corporation under supervision of Residue Chemistry Branch, HED. These chapters have undergone secondary review in the Residue Chemistry Branch (HED) and have been revised to reflect current Branch policies. The due date for these chapters is May 15, 1987. This Standard includes data available and reviewed up to April 15, 1987.

The Agency has determined that product chemistry data for all technical and manufacturing-use products must be resubmitted for each pesticide because new requirements have been introduced and previously submitted data must be updated. Therefore, the Residue Chemistry Branch will no longer evaluate previously submitted product chemistry data to determine their adequacy in meeting the requirements of Subdivision D of the Pesticide Assessment Guidelines. The Product Chemistry chapter provides a summary, but not an evaluation, of the available data for the technical grade of the active ingredient. These data are presented for informational purposes only. Attached to the Product Chemistry Chapter are comprehensive generic and product specific data requirement tables for the technical grade of the active ingredient and manufacturing-use products, respectively, of allethrin/bicallethrin.

The Product Chemistry Chapter contains Appendices A and B in which is listed Confidential Business Information and is to be protected. Only those copies of the Chapter in RCB and those sent to Arturo Castillo, The Toxicology Branch, and PMSD/ISB contain such information.

The Tolerance Assessment System figures regarding human dietary exposure to allethrin residues are not currently available. These will be presented as an addendum to the Residue Chemistry Chapter of the Standard.

Note to PM:

Residue Chemistry Branch has completed the data tables for the Residue Chemistry chapter and they are included in this package.

If you need additional input, please advise us.

cc: Ann Barton, HED (cover memo only)
Judy Heckman, HED (cover memo only)
P. Hurley, TOX, HED (with CBI Attachment)
✓ Emory Eldredge, ISB, PMSD (with CBI Attachment)

DYNAMAC
CORPORATION

Final Report

Bioallethrin
Task 1: Product Chemistry Chapter

Contract No. 68-02-4226

April 23, 1987

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

BIOALLETHRINS

PRODUCT CHEMISTRY

TASK 1

INTRODUCTION

FIFRA 3(c)(2)(A) required the Agency to establish guidelines for registe pesticides in the United States. The Agency requires registrants to pro- vide quantitative data on all added ingredients, active and inert, which are equal to or greater than 0.1% of the product by weight.

To establish the composition of products proposed for registration, the Agency requires data and information not only on the manufacturing and formulation process, but also a discussion on the formation of manufactu ng impurities and other product ingredients, intentional and unintentio Furthermore, to assure that the composition evaluated at the time of registration applicants are required to submit a statement certifying upper and lower composition limits for the added ingredients, and upper limits for some unintentional ingredients. Subdivision D of the Pesticide Assessment Guidelines (October 1982) suggests specific precision limits for ingredi based on the variability of the ingredients as a function of the manufac process.

In addition to the data on product composition, the Agency also requires data to establish the physical and chemical properties of both the pesti active ingredient and its formulations. For example, data are needed concerning the identity and physical state of the active ingredient (e.g., melting and boiling points, ambient vapor pressure and solubility Corresponding to each of the Topical Discussions listed below is the Guidelines Reference No. in "Data Requirements for Pesticide Registratio (40 CFR 158.120), which explains the minimum data the Agency will need t adequately assess the product chemistry of bioallethrins.

	Guidelines Refere No. of 40 CFR 158.120
Product Identity and Composition	61-(1-3)
Analysis and Certification of Product Ingredients	62-(1-3)
Physical and Chemical Characteristics	63-(2-21)

It should be noted that although product chemistry data may have been submitted in the past, the Agency has determined that these data must be resubmitted for each pesticide. New requirements have been introduced a previously submitted data must be updated. Therefore, in this chapter, available product chemistry data will be summarized for the technical gr

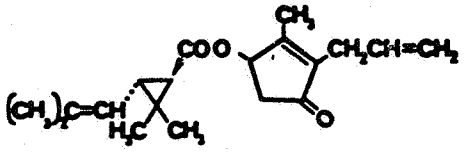
of the active ingredient only. These data will not be evaluated with regard to their adequacy in meeting the requirements of 40 CFR Part 158.120, but are presented here for informational purposes only.

PRODUCT IDENTITY AND COMPOSITION

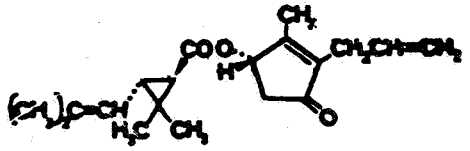
61-1. Product Identity and Disclosure of Ingredients

Bioallethrin/S-bioallethrin are the BSI-approved common names for an insecticide registered in the U.S. as technical products by Fairfield American Corp., McLaughlin Gormley King Co., Penick Corp., Penick-UCLAF Corp., Prentiss Drug and Chemical Co., and Roussel Corp. The structures of bioallethrins are depicted below.

Bioallethrin ((RS)-cyclopentenyl isomer)



Bioallethrin ((S)-cyclopentenyl isomer)



The chemical names (IUPAC) for bioallethrins are: (1RS)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)-cyclopropanecarboxylate; (1RS)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1R)-trans-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; (1RS)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1R)-trans-chrysanthemate(CA); 2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate (9CI); dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of d-trans-2,2-dimethyl-3-(2-methylpropenyl) cyclopropanecarboxylic acid; (1S)-allyl-2methyl-4-oxocyclopent-2-enyl(1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; (1S)-3-allyl-3-methyl-4-oxocyclopent-2-enyl (1R)-trans-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; (1S)-3-allyl-3-methyl-4-oxocyclopent-2-enyl (1R)-trans-chrysanthemate (CA); and 1R-[1alpha(S*),3beta]-2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate (9CI). Other names include: d-trans allethrin; allyl homolog of cinerin I; Bioallethrine; d-trans-chrysanthemum monocarboxylic ester of dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one; Esbiol; Esbiothrin; Pynamin Forte; and D-Trans.

Other identifying characteristics and codes are:

Empirical Formula:	$C_{19}H_{26}O_3$
Molecular Weight:	302.4
CAS Registry Nos.:	584-79-2 (Allethrin, Bioallethrin)
	28434-00-6 (S-Bioallethrin)
Shaughnessy Nos.:	004001/2
	004003
	004004
	004005

[The above information was obtained from the following desk references: Acceptable Common Names and Chemical Names for the Ingredient Statement on Pesticide Labels, 1979, p. 11; Farm Chemicals Handbook, 1986, p. C94; Pesticide Manufacturing and Toxic Materials Control Encyclopedia, 1980, pp. 44-47; The Pesticide Manual, 1983, pp. 48-49; and Analytical Reference Standards and Supplemental Data: The Pesticides and Industrial Chemicals Repository, 1984, pp. 14 and 21.]

Bioallethrin technical manufacturing-use products are summarized in Table 1. Refer to Confidential Appendix A for disclosure of ingredients in each product listed in the table. The products listed in Table 1 reflect percentages of cis, trans isomers of bioallethrins, not total active ingredients.

Table 1. Summary of bioallethrin technical manufacturing-use products.

Formulation	Shaughnessy No.	EPA Reg. No.	Registrant
93%T	004003	432-541	Penick Corp.
90%T	004001/2	432-587	Penick-Bio UCLAF Corp.
90%T	004001/2	655-186	Prentiss Drug & Chemical Co., Inc.
93%T	004001	1021-105[a]	McLaughlin Gormley King Co.
93%T	004001	1021-1217[b]	McLaughlin Gormley King Co.
97%T	004004	1021-1291	McLaughlin Gormley King Co.
90%T	004001	4816-78	Fairfield American Corp.
90%T	004001	4816-498	Fairfield American Corp.
90%T	004003	5086-6	Roussel Corp.
93%T	004001	5086-7	Roussel Corp.
90%T	004004	5086-8	Roussel Corp.
100%T[c]	004003	5086-12	Roussel Corp.

[a] MGK Allethrin (racemic).
[b] D-Trans Allethrin.
[c] Insufficient detail provided to verify whether this percentage reflects cis, trans bioallethrin or total active ingredients.

61-2. Discussion of Beginning Materials and Manufacturing Process

Refer to Confidential Appendix B for a discussion of the manufacturing process used to produce Roussel Corp.'s technical (T) product. This topic was not addressed for any other product listed in Table 1.

The following manufacturing process is published in Marshall Sittig's "Pesticide Manufacturing and Toxic Materials Control Encyclopedia," pp. 45-46.

> "Allethrin of high purity and biological activity not obtainable by prior methods of manufacture can be produced by the reaction of 2-allyl-3-methyl-2-cyclopenten-4-ol-1-one (allethrolone) with chrysanthemum monocarboxylic anhydride.
>
> "The chrysanthemum monocarboxylic acid which is liberated in the reaction can be separated and recovered with good efficiency for conversion to the anhydride again, as in a cyclic process.
>
> "The reaction can be readily carried out simply by heating the chrysanthemum monocarboxylic anhydride and the cyclopentenolone dissolved in a suitable solvent. In accord with well established principles, the time required for the reaction to near completion is dependent upon the temperature. In general, the reaction temperature should not exceed 200°C in order to avoid decomposition. At temperatures below 100°C, the reaction rate tends to proceed too slowly for the procedure to be practicable. A temperature of about 150° to 175°C is preferred.
>
> "As a medium for carrying out the reaction, any material which is capable of dissolving the reactants and which at the same time is not reactive with them or with the allethrin product at the temperatures employed can be used. If desired, the reaction can be carried out under reflux by choosing a solvent having a boiling temperature in the range of the reaction temperature. Representative of materials that can be employed as solvents are the following: diisopropyl ether, benzene, toluene, xylene, dibutyl ether, butyl ethyl ether, dihexyl ether. Dibutyl ether is preferred.
>
> "Usually a heating period of about 3 to 6 hours will be required for the reaction. At the end of that time the reaction mixture is diluted with additional solvent to diminish saponification of allethrin during the washing of the product with alkali. The solution is washed with alkali to remove the chrysanthemum monocarboxylic acid and then with water to remove the alkali.
>
> "The wash liquids are then extracted with more solvent to minimize the mechanical loss of allethrin. The washed oil and the extracts are then combined and stripped of low boiling material by conventional procedures, as by reduced pressures, elevated temperatures, sparging with a nonreactive gas and the like. The allethrin is obtained as a residue product."

FMC Corp. (1954; MRID 00035/71) submitted a published article authored by Sanders and Taff (1954) which contained a description of the U.S. Industrial Chemicals manufacturing process for allethrin. This continuous process is presented for informational purposes only since this description is not specific to any currently registered technical. Eighteen steps were described in detail, including reactants and intermediates, processing equipment, temperature and pressure of reactions, and structure of products. The final reaction involves combination of allethrolone, pyridine, and benzene, and gradual addition of chrysanthemum acid chloride in benzene to yield crude allethrin and HCl which reacts with the anhydrous HCl acceptor pyridine. The reactor contents are washed with water, treated with sodium carbonate, and washed with water. Benzene is removed under vacuum at <50 C, and allethrin is passed through a polishing filter.

Reactions to form allethrolone and chrysanthemum acid chloride are briefly described as follows. Allethrolone is formed by reactions 1-8 in which intermediate products are: (1) ethyl alpha-allylacetoacetate; (2) sodium alpha-allylacetoacetate; (3) allyl acetone; (4) ethyl-3-oxo-6-heptenoate; (5) potassium-3-oxo-6-heptanoate; (6) 3-oxo-6-heptenoic acid; (7) 3-hydroxy-8-nonene-2,5-dione; and (8) allethrolone. Reactions 1-3 and 5-7 are carried out at room temperature and atmospheric pressure. Conditions for reaction 4 are 60 C and 90 mm (Hg?) and for reaction 8 are 20 C and atmospheric pressure. Chrysanthemum acid chloride is formed by reactions 9-17 in which intermediate products are: (9) 2,5-dimethylhexyne-2,5-diol; (10) 2,5-dimethylhexane-2,5-diol; (11) 2,5-dimethyl-2,4-hexadiene; (12) ethyl glycine hydrochloride; (13) ethyl diazoacetate; (14) ethyl chrysanthemumate; (15) potassium chrysanthemumate; (16) chrysanthemum acid; and (17) chrysanthemum acid chloride. Reaction 10 is conducted at 100 lb/sq in, and remaining reactions occur at atmospheric pressure. Reaction temperatures are: 20 C for reactions 9, 16, and 17; 20-24 C for reaction 13; 60 C for reaction 12; 78 C for reaction 15; 90 C for reaction 10; and 130-140 C for reaction 14.

61-3. Discussion of the Formation of Impurities

This topic was not addressed for any product listed in Table 1.

ANALYSIS AND CERTIFICATION OF PRODUCT INGREDIENTS

62-1. Preliminary Analysis

This topic was not addressed for any product listed in Table 1.

62-2. Certification of Ingredient Limits

Refer to Confidential Appendix A for disclosure of ingredients in the products listed in Table 1.

62-3. Analytical Methods to Verify Certified Limits

This topic was not addressed for any product listed in Table 1.

The AOAC Official Methods of Analysis (1984, 14th ed., 6.165-6.170) describes a titrimetric method for detection of bioallethrin in technical and formulated pesticides (first action). Bioallethrin reacts quantitatively with ethylendiamine to form chrysanthemum monocarboxylic acid. Concentration of the acid is determined by titration with sodium methylate in pyridine. Independent determinations are performed to estimate concentrations of chrysanthemum monocarboxylic acid, anhydride, and acid chloride, each of which interferes with the determination of bioallethrin.

Bioallethrin and blank samples are analyzed in duplicate. Ethylene diamine is added to samples and blanks with swirling. After a 2-hour incubation at 25 ± 2 C, redistilled pyridine and thymolphthalein indicator are added. Solutions are titrated with sodium methylate (0.1 N) to the first permanent blue-green endpoint or to the first blue endpoint with colorless solutions. Concentration in millequivalents bioallethrin/gram sample is calculated with adjustment for apparent millequivalents in the blanks.

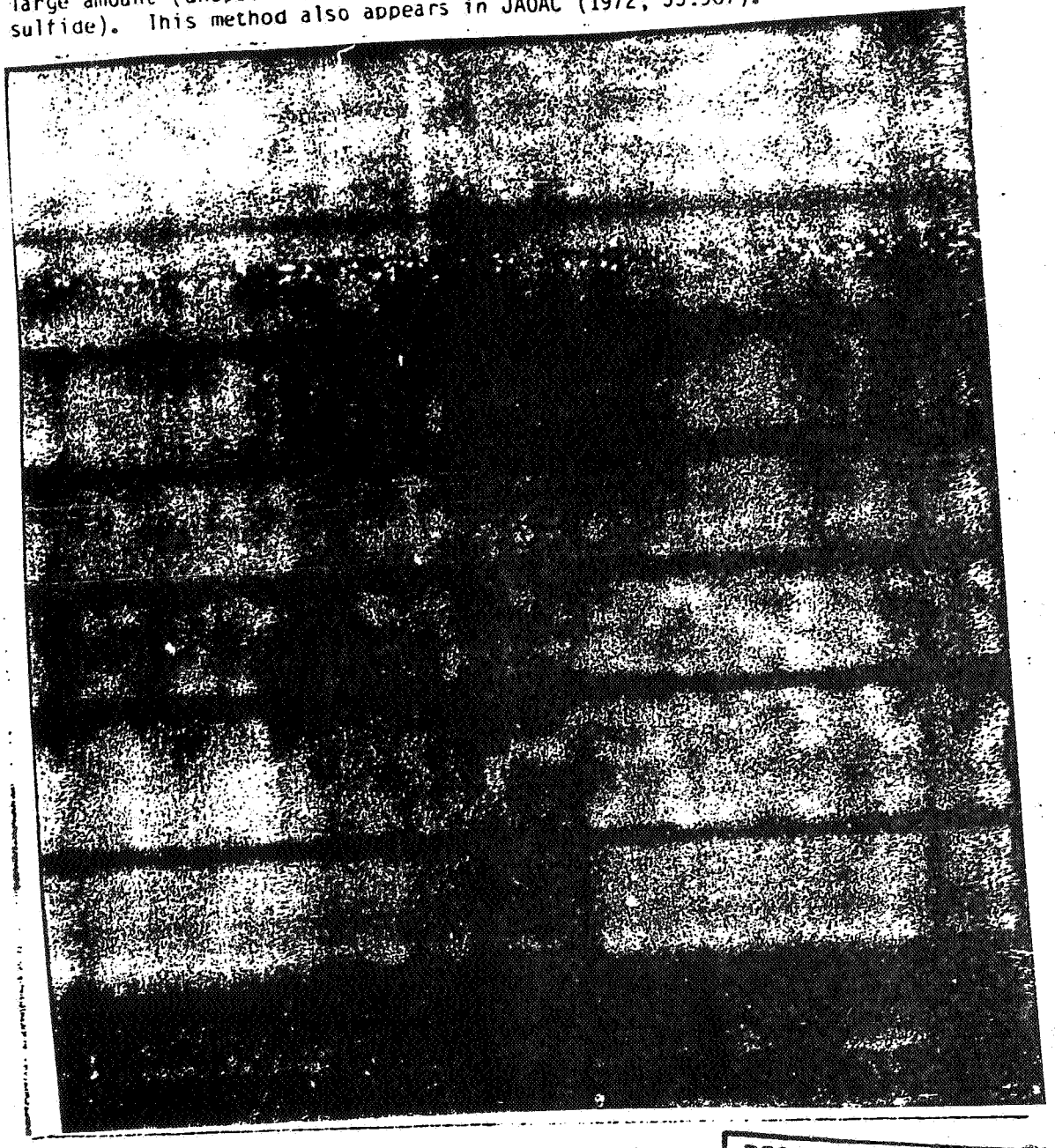
Chrysanthemum monocarboxylic acid chloride is determined by addition of technical with swirling to solutions of sodium methylate (0.1 N in pyridine) previously treated as follows. Dropwise addition of HCl (0.1 N) is made to sodium methylate until a reddish-brown color develops, and subsequently dropwise addition of potassium hydroxide (0.02 N) is made until green color first appears. Solutions of technical in treated sodium methylate are titrated with potassium hydroxide (0.02 N) to the first green endpoint within 5 minutes of sample addition using a blank solution of treated sodium methylate as a reference. Concentration is reported in millequivalents of chrysanthemum monocarboxylic acid chloride/gram sample.

Chrysanthemum monocarboxylic acid is determined by addition of the technical sample to a solution of anhydrous alcohol previously treated with alpha-naptholbenzein and cooled in an ice bath to 0 (C or F unspecified) and subsequently neutralized by dropwise addition of sodium hydroxide (0.02 N) to the bright green endpoint. The solution of technical in treated alcohol is immediately titrated with sodium hydroxide (0.02 N) to the first bright green endpoint. Concentration in millequivalents of chrysanthemum monocarboxylic acid is determined by subtraction of the concentration of chrysanthemum monocarboxylic acid chloride determined in method 6.167 from millequivalents detected in 6.168, and by multiplication by a constant.

Chrysanthemum monocarboxylic anhydride is determined by addition of technical with swirling to a solution of redistilled morpholine in anhydrous methanol. Mixed indicator solution, containing dimethyl yellow and methylene blue in anhydrous methanol, is added after five minutes to sample and blank solutions. Solutions are titrated with HCl (0.1 N) until color by transmitted light changes from green to faint red. The concentration of the anhydride is adjusted for apparent millequivalents in the blank solution and for the concentration of chrysanthemum monocarboxylic acid chloride determined by 6.167.

These methods also appear in JAOAC (1957; 40:732). We note that the titrimetric methods may not be suitable for enforcement of certified limits.

The AOAC Official Methods of Analysis (1984, 14th ed., 6.171-6.175) describes a GLC method for detection of bioallethrin in technical and formulated pesticides (final action). Bioallethrin is diluted in acetone containing dibutyl phthalate as the internal standard and analyzed by GLC using a column packed with 5% OV-1 on 80-100 mesh Chromosorb W(HP) and flame ionization detection (FID). Concentration is determinated by comparison of peak heights of standard and sample. This procedure is not applicable to determination of allethrin in formulations containing a large amount (unspecified) of MGK Repellent 874 (2-hydroxyethyl-n-octyl sulfide). This method also appears in JAOAC (1972; 55:907).



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PHYSICAL AND CHEMICAL CHARACTERISTICS

Summarized in Table 2 are several physicochemical properties of an unspecified, an unregistered, and a 93% T.

Table 2. Physicochemical properties of an unspecified, an unregistered, and a 93% T.

Guidelines Reference No. of 40 CFR 158.120; Name of Property	Description	Product[a]	Bibliographic Citation (MRID or Reg. Jacket No.)
63-2. Color	Pale yellow	MGK	00122932
	Yellow-orange	R	432-541
	Slightly brownish	S	00061220
63.3. Physical State	Viscous oil	R	432-541
	Liquid, clear oil	S	00061220, 00075[illegible]
63-4. Odor	Mild, unobjectionable	S	00061220
	Slightly aromatic	MGK	00122932
63-5. Boiling Point	135-138 C at 0.25 mm Hg	S	00061220
63-7. Specific Gravity	1.000-1.010 at 20 C	MGK	00122932
	1.000-1.010 at 20 C	R	432-541
	1.005-1.015 at 20 C	S	00061220
63-8. Solubility	Complete at 10% in hexane	R	432-541
	Insoluble in water; miscible with petroleum oils; "perfectly soluble" in paraffinic and aromatic hydrocarbons	S	00061220
63-13. Stability	Unstable in light and heat	S	00061220

[a] MGK = Unspecified McLaughlin Gormley King Co. T; R = Roussel-UCLAF 93% T; S = Sumitomo Chemical Co. unregistered T.

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TABLE A. GENERIC DATA REQUIREMENTS FOR THE TECHNICAL GRADE OF THE ACTIVE INGREDIENT

Data Requirement	Composition[a]	Does EPA Have Data to Satisfy This Requirement?[b]	Bibliographic Citation[b]	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Frame For Data Submission
158.120 Product Chemistry					
Product Identity and Composition					
61-2 - Description of Beginning Materials and Manufacturing Process	TGAI	No	N/A	Yes[c]	6 months
61-3 - Discussion of Formation of Impurities	TGAI	No	N/A	Yes[d]	6 months
Analysis and Certification of Product Ingredients					
62-1 - Preliminary Analysis of Product Samples	TGAI	No	N/A	Yes[e]	12 months
Physical and Chemical Characteristics					
63-2 - Color	TGAI	No	N/A	Yes[f]	6 months
63-3 - Physical State	TGAI	No	N/A	Yes[f]	6 months
63-4 - Odor	TGAI	No	N/A	Yes[f]	6 months
63-5 - Melting Point	TGAI	No	N/A	Yes[f,g]	6 months
63-6 - Boiling Point	TGAI	No	N/A	Yes[f,h]	6 months
63-7 - Density, Bulk Density, or Specific Gravity	TGAI	No	N/A	Yes[f]	6 months

(continued, footnotes follow.)

TABLE A. (CONTINUED).

Data Requirement	Composition[a]	Does EPA Have Data to Satisfy This Requirement?[b]	Bibliographic Citation[b]	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Frame For Data Submission
158.120 Product Chemistry (continued)					
63-8 - Solubility	TGAI or PAI	No	N/A	Yes[f]	6 months
63-9 - Vapor Pressure	TGAI or PAI	No	N/A	Yes[f]	6 months
63-10 - Dissociation Constant	TGAI or PAI	No	N/A	Yes[f]	6 months
63-11 - Octanol/Water Partition Coefficient	PAI	No	N/A	Yes[f,i]	6 months
63-12 - pH	TGAI	No	N/A	Yes[f,j]	6 months
63-13 - Stability	TGAI	No	N/A	Yes[f]	6 months
Other Requirements:					
64-1 - Submittal of samples	N/A	N/A	N/A	No	

[a] Composition: TGAI = technical grade of the active ingredient; PAI = pure active ingredient.

[b] Not applicable. Although product chemistry data may have been submitted in the past, the Agency has determined that these data must be resubmitted for each pesticide. New requirements have been introduced and previously submitted data must be updated. Therefore, bibliographic citations for the old data are not applicable.

[c] Complete information must be provided regarding the nature of the process (batch or continuous), the relative amounts of beginning materials and the order in which they are added, the chemical equations for each intended reaction, equipment used to produce each intermediate and the final product, reaction conditions, the duration of each step of the process, purification procedures, and quality control measures. In addition, the name and address of the manufacturer, producer, or supplier of each beginning material must be provided, along with information regarding the properties of each beginning material used to manufacture each product.

TABLE A (Continued).

[d] A detailed discussion of all impurities tnat are or may be present at ≥0.1%, based on knowledge of the beginning materials, chemical reactions (intended and side) in the manufacturing process, and any contamination during and after production must be submitted.

[e] Five or more representative samples must be analyzed for the amount of active ingredient and each impurity for which a certified limit is required. Complete validation data (accuracy, precision) must be submitted for each analytical method used.

[f] Physicochemical characteristics (color, physical state, odor, melting point, boiling point, specific gravity, solubility, vapor pressure, dissociation constant, K_{OW}, pH, and stability) as required in 40 CFR 158.120 and more fully described in the Pesticide Assessment Guidelines, Subdivision D must be submitted.

[g] Data needed if the technical chemical is a solid at room temperature.

[h] Data needed if the technical chemical is a liquid at room temperature.

[i] Required if the technical chemical is organic and non-polar.

[j] Required if the test substance is dispersible with water.

TABLE B. PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING USE PRODUCTS

Data Requirement	Composition[a]	Does EPA Have Data to Satisfy This Requirement?[b]	Bibliographic Citation[b]	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Frame For Data Submission
158.120 Product Chemistry					
Product Identity and Composition					
61-1 - Product Identity and Disclosure of Ingredients	MP	No	N/A	Yes[c]	6 months
61-2 - Description of Beginning Materials and Manufacturing Process	MP	No	N/A	Yes[d]	6 months
61-3 - Discussion of Formation of Impurities	MP	No	N/A	Yes[e]	6 months
Analysis and Certification of Product Ingredients					
62-1 - Preliminary Analysis of Product Samples	MP	No	N/A	Yes[f]	12 months
62-2 - Certification of Ingredient Limits	MP	No	N/A	Yes[g]	12 months
62-3 - Analytical Methods to Verify Certified Limits	MP	No	N/A	Yes[h]	12 months
Physical and Chemical Characteristics					
63-2 - Color	MP	No	N/A	Yes[i]	6 months
63-3 - Physical State	MP	No	N/A	Yes[i]	6 months
63-4 - Odor	MP	No	N/A	Yes[i]	6 months
63-7 - Density, Bulk Density, or Specific Gravity	MP	No	N/A	Yes[i]	6 months

(continued, footnotes follow.)

TABLE B. (CONTINUED).

Data Requirement	Composition[a]	Does EPA Have Data to Satisfy This Requirement?[b]	Bibliographic Citation[b]	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Frame For Data Submission
158.120 Product Chemistry (continued)					
63-12 - pH	MP	No	N/A	Yes[i,j]	6 months
63-14 - Oxidizing or Reducing Action	MP	No	N/A	Yes[i,k]	6 months
63-15 - Flammability	MP	No	N/A	Yes[i,l]	6 months
63-16 - Explodability	MP	No	N/A	Yes[i,m]	6 months
63-17 - Storage Stability	MP	No	N/A	Yes[i]	15 months
63-18 - Viscosity	MP	No	N/A	Yes[i,n]	6 months
63-19 - Miscibility	MP	No	N/A	Yes[i,o]	6 months
63-20 - Corrosion Characteristics	MP	No	N/A	Yes[i]	15 months
Other Requirements:					
64-1 - Submittal of samples	N/A	N/A	N/A	No	

[a] Composition: MP = Manufacturing Use Product.

[b] Not applicable. Although product chemistry data may have been submitted in the past, the Agency has determined that these data must be resubmitted for each pesticide. New requirements have been introduced and previously submitted data must be updated. Therefore, bibliographic citations for the old data are not applicable.

[c] The chemical name and nominal concentration of each impurity for which a certified limit is required must be submitted. In addition, the chemical name, nominal concentration, Chemical Abstracts (CAS) Registry Number, and purpose of the active ingredient and each intentionally added inert must be provided. For the active ingredient, the following must also be provided: the product name, trade name, and common name; the molecular, structural, and empirical formulas; the molecular weight or weight range; and any experimental or internally assigned company code numbers.

TABLE B (Continued).

d Complete information must be provided regarding the nature of the process (batch or continuous), the relative amounts of beginning materials and the order in which they are added, the chemical equations for each intended reaction, equipment used to produce each intermediate and the final product, reaction conditions, the duration of each step of the process, purification procedures, and quality control measures. In addition, the name and address of the manufacturer, producer, or supplier of each beginning material must be provided, along with information regarding the properties of each beginning material used to manufacture each product.

e A detailed discussion of all impurities that are or may be present at ≥0.1%, based on knowledge of the beginning materials, chemical reactions (intended and side) in the manufacturing process, and any contamination during and after production must be submitted.

f Five or more representative samples must be analyzed for the amount of active ingredient and each impurity for which a certified limit is required. Complete validation data (accuracy, precision) must be submitted for each analytical method used.

g Upper and lower limits for the active ingredient and each intentionally added inert, and upper limits for each impurity present at ≥0.1% (w/w) and each "toxicologically significant" impurity present at <0.1% (w/w) must be provided, certified, and validated by sample analysis using analytical procedures for which accuracy and precision data have been provided. Limits for impurities not associated with the active ingredient need be provided only if they are considered to be of toxicological significance, regardless of the concentration at which they are present. [We defer to the Toxicology Branch regarding the toxicological significance of (i) impurities associated with the active ingredient present at <0.1% (w/w) and (ii) impurities not associated with the active ingredient.] Certifications must be submitted on EPA Form 8570 Rev. 2-85.

h Analytical methods must be provided to determine the active ingredient, and each toxicologically significant impurity and intentionally added inert for which certified limits are required. Each method must be accompanied by validation studies indicating its accuracy and precision. These methods must be suitable for enforcement of certified limits. [RCB defers to the TOX Branch regarding the toxicological significance of impurities and intentionally added inerts for which certified limits are required.]

Table B. (Continued).

[i] Physicochemical characteristics (color, physical state, odor, specific gravity, pH, oxidizing or reducing action, flammability, explodability, storage stability, viscosity, miscibility, and corrosion characteristics) as required in 40 CFR 158.120 and more fully described in the Pesticide Assessment Guidelines, Subdivision D must be submitted.

[j] Required if the test substance is dispersible with water.

[k] Required if the product contains an oxidizing or reducing agent.

[l] Required if the product contains combustible liquids.

[m] Required if the product is potentially explosive.

[n] Required if the product is a liquid.

[o] Required if the product is a liquid and is to be diluted with petroleum solvents.

References (not used):

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References (not used/not cited):

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GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN

Data Requirement	Test Substance[1]	Does EPA Have Data?	Bibliographic Citation	Must Additional Data Be Submitted?	Time Frame for Submission[2]
158.125 Residue Chemistry					
171-2. Chemical identity[3]					
171-3. Directions for use		(See Index)			
171-4. Nature of the residue (Metabolism)					
- Plants	PAIRA	No	—	Yes[4]	18 Months
- Livestock	PAIRA	No	—	Yes[5][6]	18 Months
171-4. Residue analytical methods					
	TGAI & Metabolites	Yes	00031930, 00035929, 00064646, 00013587, King Zee, 1980.	Yes[7]	15 Months
171-4. Storage stability data	PAI or TEP, and metabolites	No		Yes[8]	18 Months

(Continued).

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GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued)

Data Requirement	Test Substance[1]	Does EPA Have Data?	Bibliographic Citation	Must Additional Data Be Submitted?	Time Frame for Submission[2]
171-4. Magnitude of the Residue					
- Crop field trials					
- alfalfa, apples, beans, broccoli, Brussels sprouts, cabbage, cauliflower, celery, citrus, clover, collards, cucurbits, endive, horseradish, kale, kohlrabi, lettuce, mustard greens, parsley, peaches, pears, peas, peppers, potatoes, radishes, rutabagas, sorghum, spinach, sugarcane, tomatoes, and turnips	TEP	No		Yes[9]	18 Months
- artichokes (Jerusalem), carrots, chicory, corn, garlic, leeks, onions, parsnips, salsify, shallots, and sweet potatoes	TEP	No		Yes[10]	18 Months
- Mushrooms	TEP	No		Yes[11]	18 months

Continued.

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued)

Data Requirement	Test Substance[1]	Does EPA Have Data?	Bibliographic Citation	Must Additional Data Be Submitted?	Time Frame for Submission[2]
- Postharvest treatment of fruits and vegetables					
- apples, blackberries, blueberries, boysenberries, cherries, crabapples, currants, dewberries, grapes, muskmelons, oranges, peaches, pears, pineapples, plums, and raspberries	TEP	No		Yes[12]	18 Months
- figs, gooseberries, guavas, loganberries, mangoes, and tomatoes	TEP	No		Yes[13]	18 Months
- Stored commodities					
- barley, corn, oats, rye, sorghum, and wheat	TEP	No		Yes[14]	18 Months
- dried fruit	TEP	No		Yes[15]	18 Months
- stored foods	TEP	No		Yes[16]	18 Months
- Processing Studies					
- apples, oranges, sorghum, sugarcane tomatoes	EP	No		Yes[17]	24 Months

(Continued)

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued)

Data Requirement	Test Substance[1]	Does EPA Have Data?	Bibliographic Citation	Must Additional Data Be Submitted?	Time Frame for Submission[2]
- grapes, pineapples, plums	EP	No		Yes[18]	24 Months
- field corn and wheat	EP	No		Yes[19]	24 Months
- Meat/milk/poultry/eggs	TGAI or Plant Metabolites	No		Yes[20]	18 Months
- Food handling	EP	No		Yes[21][22]	12 Months

1/ Test Substance: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabeled; TEP = Typical end-use product; EP = end-use product.

2/ Data must be submitted within the indicated time frame, based on the date of this Guidance Document.

3/ Refer to Product Chemistry Data Requirement tables.

(Continued).

4/ The uptake, distribution, and metabolism of [^{14}C]allethrin in a tree fruit crop (pome, stone, or citrus), a legume or fruiting vegetable (beans or tomatoes) and a leafy or brassica leafy vegetable (lettuce or cabbage). [^{14}C]allethrin (004001 - a mixture of eight isomers) must be applied foliarly several times up to and including the day of harvest at rates sufficiently high to permit complete characterization of ^{14}C-residues. The identities and quantities of residues in or on mature plant parts must be determined in order to elucidate terminal residues. Representative samples from these tests must also be analyzed by enforcement methods to ascertain that the methods are adequately capable of quantifying all residues of concern. To avoid unnecessary expense and repetition of residue tests (field trials, processing studies, postharvest use trials, and food handling establishment use tests), RCB recommends that the required plant metabolism data be submitted for review prior to initiation of residue trials.

5/ Metabolism studies utilizing ruminants and poultry. Animals must be dosed orally for a minimum of 3 days with [^{14}C]allethrin (004001 - a mixture of eight isomers) at a level sufficient to make residue identification and quantification in tissues and milk possible. Milk and eggs must be collected twice a day during the dosing period. Animals must be sacrificed within 24 hours of the final dose. The distribution and characterization of residues must be determined in milk, eggs, liver, kidney, muscle, and fat.

6/ Metabolism studies using cattle, poultry and swine reflecting <u>direct</u> animal treatment. These data are needed because allethrin (004001) is registered for use as a space spray in farm animal quarters and as a direct treatment to horses, and bioallethrin (004003) is registered for use as a space spray in milking houses. Animals must be sprayed daily for 28 days using [^{14}C]allethrin (004001 - a mixture of eight isomers) at a rate sufficiently high to permit complete characterization of ^{14}C-residues and sacrificed within one day of the final application. ^{14}C-Residues must be quantified and characterized in muscle, fat, liver, kidney, milk and eggs. Eggs and milk must be collected twice daily throughout the treatment period.

7/ Additional residue and validation data and appropriate methods may be required if requested metabolism/degradation studies reveal additional metabolites of toxicological concern. All residue data submitted in response to this Standard must be accompanied by a description of the analytical method used and method validation data (sensitivity, accuracy, and precision).

8/ All residue data requested in this Standard must be accompanied by information specifying the storage intervals and conditions for samples analyzed. Data must also be submitted depicting the storage stability of the residues of concern under the same conditions and time intervals specified. In laboratory tests using fortified samples, the pure active ingredient and pure metabolites (if necessary) must be used. However, if field weathered samples are used, the test substance must be a typical end-use product.

Continued.

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued)

9/ Data depicting allethrin residues of concern in or on (i) greenhouse and field grown snap beans, dry beans and bean vines (field-grown only), broccoli, cabbage, collards, lettuce (leaf and head - with and without wrapper leaves), radishes, and tomatoes harvested immediatly after the last of multiple foliar treatments of the 2.5% EC formulation at 36 fl. oz. product/100 gal water/A; (ii) apples, oranges and peaches harvested immediatly after the last of multiple foliar treatments of the 1% EC formulation at 1 quart product/A using both high and low (2 gal/A) volume ground equipment in separate tests; (iii) celery and horseradish harvested immediatly after the last of multiple foliar treatments of the 1% EC formulation at 1.5 pints product/A in 1 gal water/A and; to support a FL 24(c) label (FL780061), (iv) alfalfa forage and hay, cucumbers, melons, summer squash, potatoes, grain sorghum (grain, forage, fodder, silage and hay), sweet sorghum (seed, forage and fodder), and sugarcane (cane and forage) harvested one day after multiple foliar applications, made at 5-day intervals, of the 0.9% EC formulation at 2 pints product/A in 1 gal water/A. A maximum number of applications per season must be proposed for all uses and reflected in the submitted data. Tests must be conducted in states that represent the major growing regions for each crop according to the latest edition of Agricultural Statistics (USDA) or the Census of Agriculture (U.S. Dept. of Commerce), except to support the FL 24(c) label (tests need be conducted in FL only). [The data requested here for apples, broccoli, lettuce, collards, tomatoes, radishes, alfalfa, and beans will be used to predict residues in or on pears, Brussels sprouts, cauliflower, kohlrabi, endive, kale, mustard greens, parsley, spinach, peppers, rutabagas, turnips, clover, and peas.] A tolerance proposal is required for each of these commodities.

10/ The Registrant(s) must propose a preharvest use on Jerusalem artichokes, sugar beets, carrots, chicory, corn (sweet and field), garlic, leeks, onions, parsnips, salsify, shallots, and sweet potatoes accompanied by appropriate residue data (currently, an entry exists in 40 CFR 180.1002 for these commodities but no registered uses on them exist). Processing studies must be submitted for field corn (crude and refined oil, grain dust, and milling products [starch, grits, meal, flour]), and sugar beets (dehydrated pulp, molasses and refined sugar). If the rate proposed (i) on Jerusalem artichokes and sweet potatoes is no higher than that registered for use on potatoes; and (ii) on sugar beets, parsnips, salsify and carrots no higher than on radishes, no residue data for these crops need be submitted (processing data would still be required). Also, if the uses proposed on garlic, leeks, onions and shallots are identical, data need be submitted only for onions (green and bulb). Appropriate tolerances must be proposed.

11/ Data depicting allethrin residues of concern in or on mushrooms grown in mushroom houses in which multiple premise treatments have been made with the 1.25% RTU as a 1.25% finished spray. A maximum number of applications must be proposed and supporting data submitted. An appropriate tolerance must be proposed.

Continued.

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued).

12/ Data depicting allethrin residues of concern in or on apples, blackberries, plums, blueberries, grapes, muskmelons, oranges, peaches, and pineapples. Samples must be taken (in separate tests) immediately following a 0.012% emulsion dip treatment with the 2.5% EC formulation. [Data required for apples, blackberries, blueberries and plums will be used to predict residues in or on boysenberries, dewberries, raspberries, pears, crabapples, cherries and currants.]

13/ The Registrant(s) must propose a postharvest use on figs, gooseberries, guavas, loganberries, mangoes, and tomatoes accompanied by residue data in support of the established tolerances for residues in or on these commodities. Processing data must be submitted for figs (dried figs). If the rate proposed on gooseberries and loganberries is no higher than that registered for use on blueberries and blackberries, then no residue data for gooseberries or loganberries need be submitted. If these data and/or proposed uses are not submitted, the tolerances for allethrin residues in/on the crops will be revoked.

14/ Data depicting allethrin residues of concern in or on corn and wheat treated with an EC, SC/L, and RTU formulation in separate tests at 5 gal/1,000 bu (0.5% finished spray) in such a way that the grain will be tumbled and mixed before it enters the storage bin. The surface of the binned grain must also be treated with the same formulations (in separate tests) at 1 gal/1,000 sq ft of grain (0.5% finished spray every 30 days from the time of storage until early fall). The storage bin must have a surface application of the 15% EC at 1 gal/750 sq ft just prior to the storage of the grain. Samples must be collected on the day they enter the storage bin and on the day of the last surface treatment in early fall. [Required data for corn and wheat will be used to predict residues in or on grain sorghum, oats, rye, and barley.]

15/ Data depicting allethrin residues of concern in or on dried fruit (dried apples, prunes, raisins, bananas, figs, dates) sampled immediately following treatment with a 5% SC/L at 1 fl. oz/1,000 cu ft and a 0.326% RTU at 1 gal/50,000 cu ft (in separate tests). These formulations are to be discharged as a fine mist above dried fruit. The registrant(s) must propose an appropriate tolerance for allethrin residues in stored dried fruit.

16/ Data depicting allethrin residues of concern in representative raw agricultural commodities (dried beans, cocoa beans, coffee beans, corn, nuts, peanuts, and soybeans) collected immediately following an indoor space spray with the 5% SC/L and a RTU formulation at 1 fl. oz/1,000 cu ft. The registrant(s) must propose an appropriate tolerance for allethrin residues in stored raw agricultural commodities.

Continued.

GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN (Continued).

17/ Data depicting allethrin residues of concern in the following processed commodities obtained from raw agricultural commodities bearing measurable field-weathered residues: wet and dry pomace and juice from apples; dried pulp, oil, molasses, and juice from oranges; flour, starch and grain dust from grain sorghum; syrup from sweet sorghum; molasses, refined sugar, and bagasse from sugarcane; and wet and dry pomace, puree, catsup, and juice from tomatoes. If residues concentrate, appropriate food/feed aditive tolerances must be proposed.

18/ Data depicting allethrin residues of concern in the following processed commodities obtained from postharvest-treated raw agricultural commodities: raisins, wet and dry pomace, raisin waste and juice from grapes; bran and juice from pineapples; and dried prunes from plums. If residues concentrate in these processed commodities, appropriate food/feed additive tolerances must be proposed.

19/ Data depicting allethrin residues of concern in grain dust and milled products of field corn and wheat (including the wet milled products of corn - starch, crude oil and refined oils, the dry milled products of corn - grits, meal, flour, crude and refined oils; and bran, flour, middlings and shorts for wheat). Samples must be processed from grains bearing measurable weathered residues from postharvest treatments. If concentration occurs, appropriate food/feed additive tolerances must be proposed.

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20/ Data requirements regarding the magnitude of the residues in animal products will not be determined until all requested data regarding metabolism in animals and magnitude of residues in feed items have been received.

21/ Data depicting residues of concern in food products resulting from applications of allethrin in food service, food manufacturing, and food processing establishments (two representative types of each food handling establishment as listed in Table 1 of Subdivision O [Residue Chemistry] of the Pesticide Assessment Guidelines). Tests are required in these establishments utilizing an SC/L and RTU formulation as a general contact spray and space spray (in separate tests) in 12.5% ai finished spray. Tests conducted must be representative examples of worst-case scenarios for potential residue contamination of food products which include the following: (i) particulate aerosol contact with packaged products or unwrapped fresh produce present at the time of treatment; (ii) contact of packaged foods with treated surfaces, such as flour sacks stacked on treated floor surfaces in storage areas; (iii) accidental treatment of food work surfaces and subsequent contact of food before surfaces are cleaned; (iv) treatment occurring near stacks of new or cleaned product containers that are filled without being cleaned; and (v) tracking of residues by insects or rodents from treated areas to food or food contact surfaces. Exposure situations in grocery stores and restaurants must include a representative range of foods such as oily foods, baked cereal products, raw and cooked meats, and fresh fruits and vegetables.

22/ The registrant(s) must propose a tolerance for residues of bioallethrin in food/feed exposed during or following treatment of food/feed handling establishments.

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAY 14 1987

MEMORANDUM

SUBJECT: Registration Standard for Bioallethrin Group Insecticides (Exposure Assessment Branch Chapter)

FROM: Arthur O. Schlosser Chemist, RS #3
Exposure Assessment Branch, HED (TS-769C)

TO: Arturo E. Castillo, Product Manager #17
Insecticide Branch, RD (TS-767C)

THRU: Robert W. Holst, Acting Chief
Exposure Assessment Branch, HED (TS-769C)

Attached are the EAB Tasks I and 2, and Table A (Generic Data Requirements) for the pesticide chemicals: Allethrin (allyl homolog of cinerin 1), d-trans Allethrin (allyl homolog of cinerin I)(Bioallethrin), d-trans Chrysanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (S-Bioallethrin) and d-cis/trans Allethrin.

Attachment

cc: Amy Rispin

REGISTRATION STANDARD FOR THE BIOALLETHRIN GROUP PESTICIDES

EXPOSURE ASSESSMENT BRANCH CHAPTER

ALLETHRIN	004001
BIOALLETHRIN	004003
S-BIOALLETHRIN	004004
D-CIS/TRANS ALLETHRIN	004005

Prepared by:

Arthur O. Schlosser, Chemist

Exposure Assessment Branch
Hazard Evaluation Division
U.S. Environmental Protection Agency
Washington, D.C.

May 1, 1987

TASKS 1 and 2

REGISTRATION STANDARD FOR THE BIOALLETHRIN GROUP

(1) Bioallethrin [d-trans allethrin(allyl homolog of cinerin I)]

EPA Shaughnessy Code 004003

INTRODUCTION

Bioallethrin[d-trans allethrin(allyl homolog of cinerin I)] is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten -1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial food crops(e.g. asparagus, beans, corn, tomatoes and non-bearing cranberries and citrus fruits),terrestrial nonfood crops(e.g. ornamental plants and forest trees), greenhouse food crops(e.g. asparagus, beans, corn, peppers and tomatoes), greenhouse nonfood crops(e.g. ornamental plants), domestic outdoor(domestic dwellings, outdoor) and many domestic,commercial and industrial indoor uses. Bioallethrin formulations almost always contain a synergist and one or more otner active ingredients. End use formulations include dusts (0.15-1.8%), impregnated materials (0.125-4.8%), EC(0.837-6%), SC/L (0.06%,0.324%), RTU (0.05-0.6%) and pressurized liquids (0.03-1.2%).

TASK I No data were available for review.

TASK II

EXECUTIVE SUMMARY No data were reviewed.

RECOMMENDATIONS

Available data are insufficient to fully assess the environmental fate and transport of, and the potential exposure of humans and nontarget organisms to bioallethrin. A summary of registration requirements (Subdivision N) for terrestrial food crop, terrestrial nonfood crop, greenhouse food crop, greenhouse nonfood crop, domestic outdoor and indoor use sites is given below:

Hydrolysis studies: No data were reviewed, but all data are required.

Photodegradation studies in water: No data were reviewed, but all data are required.

Photodegradation studies on soil: No data were reviewed, but all data are required.

Photodegradation studies in air: No data were reviewed, however no data are required.

Aerobic soil metabolism studies: No data were reviewed, but all data are required.

Anaerobic soil metabolism studies: No data were reviewed, but all data are required.

Aerobic aquatic metabolism studies: No data were reviewed, however no data are required because there are no aquatic uses for the active ingredient.

Anaerobic aquatic metabolism studies: No data were reviewed, however no data are required because there are no aquatic or forestry uses for the active ingredient.

Leaching and adsorption/desorption studies: No data were reviewed, but all data are required. Adsorption/desorption(batch equilibrium)data are specifically needed to support the use on cranberries.

Laboratory volatility studies: No data were reviewed, however no data are required.

Field volatility studies: No data were reviewed, however no data are required.

Terrestrial field dissipation studies: No data were reviewed, but all data are required.

Aquatic field dissipation studies: No data were reviewed, however no data are required since there are no aquatic uses for the active ingredient.

Forestry dissipation studies: No data were reviewed, no data are required because there are no forestry uses for the active ingredient.

Dissipation studies for combination products and tank mix uses: No data were reviewed; however, no data are required because data requirements for combination products and tank mix uses are currently not being imposed.

Long-term field dissipation studies: No data were reviewed, but all data may be required unless field residues reach 50% dissipation prior to recommended subsequent application to the same site, or if aerobic soil metabolism studies indicate that residues are greater than 50% of initial application at the time of subsequent application.

Confined accumulation studies on rotational crops: No data were reviewed, but all data are required.

Field accumulation studies on rotational crops: No data were reviewed; however this data requirement is deferred pending evaluation of the results of the confined rotational crop study.

Accumulation studies on irrigated crops: No data were reviewed, but all data are required to support the use on cranberries.

Laboratory studies of pesticide accumulation in fish: No data were reviewed, but all data were required.

Field accumulation studies on aquatic nontarget organisms: No data were reviewed, but all data are required to support the use on cranberries.

Reentry studies:

Under 40 CFR § 158.140, reentry data are required for bioallethrin [d-trans allethrin (allyl homolog of cinerin I)] if the pesticide and its use patterns meet certain criteria. Those criteria include both toxicity and exposure. The "When required" paragraphs of Subdivision K discuss the circumstances under which § 158.140 requires reentry data.

The toxicity criteria for requirement of a proposed reentry interval and supporting data, are as follows:

-The acute dermal toxicity of the technical grade of active ingredient is less than 200 mg/kg (body weight); or
-The acute inhalation toxicity of the technical grade of active ingredient is less than 200 mg/m^3 (for a one hour exposure); or
-The acute oral toxicity of the technical grade of active ingredient is less than 50 mg/kg (body weight); or
-Neurotoxic, teratogenic, or oncogenic effects or other adverse effects as evidenced by subchronic, chronic and reproduction studies would be expected from entry of persons into treated sites; or
-The Agency recieves other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects on persons entering treated sites.

These toxicity criteria are based on toxicities of the technical pesticide and its toxic alteration products. This is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

The exposure criteria are based on the pesticide's use types. The use type criteria for requirement of a proposed reentry interval and the supporting data are listed in 40 CFR § 158.140 and are discussed in § 130-3 of Subdivision K. These use types are characterized by a high likelihood of dermal or inhalation exposure of persons who enter sites included in these

classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has become airborne.

Reentry data are required under 40 CFR § 158.140 only when both the toxicity and the exposure criteria are met. When reentry data are required, those data are to support the registration of the end-use product and each manufacturing-use product used to formulate each end-use product. Data will normally be gathered by the manufacturer of the manufacturing-use product but using an end-use product for the tests.

Bioallethrin does meet the exposure criteria of 40 CFR 158.140 in that it is used on crops where human exposure could occur, but available toxicology data do not indicate that it meets any of the toxicity criteria. However, if the results of the toxicology testing requirements indicate that bioallethrin does meet any of the toxicity criteria reentry data will be required. No data are required at this time.

Spray drift studies: No data were reviewed, however no data are required.

GROUNDWATER No data are currently available to assess the potential for bioallethrin to contaminate groundwater.

LABEL REQUIREMENTS:

ROTATED CROPS: No rotational crop restriction is being imposed at this time since data are currently not available to form the basis for a restrictive interval. When the required data have been received and evaluated a restriction may be imposed.

IRRIGATED CROPS: No restriction is being imposed on the use of water used to irrigate or flood treated areas since data are currently not available to form the basis for a restrictive interval. When the required data have been received and evaluated a restriction may be imposed.

REFERENCES

The following study was not reviewed because it contains product chemistry data only:

Mitchell, L. 1961. The effect of ultraviolet light (2537 A) on 141 pesticide chemicals by paper chromatography. J. A.O.A.C. 44(4):643-651, 686, 712. (00158197)

The following study was not reviewed because it contains product chemistry data and a photodegradation on glass experiment only:

Miskus, R. and T. Andrews. 19??. Stabilization of thin films of pyrethrins and allethrin. Pyrethrum Post:135-136. Incomplete; also In unpublished submission received Jan. 21, 1977 under 6296-24; submitted by Nutrilite Products, Inc., Buena Park, CA; CDL:229731-B. (00113574)

The following study was not reviewed because it contains analytical methodology, a photodegradation on glass experiment, product chemistry, and directions for use only:

Sumitomo Chemical Co., Ltd. 1972. Chemical study--pynamin forte. Compilation; unpublished study received Nov. 26, 1973 under 10308-3; CDL:026202-A. (00122922)

The following study (duplicate hardcopies received) was not reviewed because it contains bioassays, residue chemistry, and a photodegradation on glass experiment only:

Elliott, M., A.W. Farnham, N.F. Janes, et al. 1973. NRDC 143: A more stable pyrethroid. Pages 721-728, In Proceedings, 7th British Insecticide and Fungicide Conference. N.P. Also In unpublished submission received Feb. 3, 1977 under 10182-EX-7; submitted by ICI Americas, Inc., Wilmington, DE; CDL:228608-B. (0006649 and 00060035)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-trans Allethrin (allyl homolog of cinerin I)
(Bioallethrin)

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.130 Environmental Fate					
DEGRADATION STUDIES-LAB:					
161-1 - Hydrolysis	TGAI or PAIRA	A,B,E,F,H	NO	-	YES
Photodegradation					
161-2 - In water	TGAI or PAIRA	A,B	NO	-	YES
161-3 - On soil	TGAI or PAIRA	A	NO	-	YES
161-4 - In Air	TGAI or PAIRA	A		-	(4)
METABOLISM STUDIES-LAB:					
162-1 - Aerobic Soil	TGAI or PAIRA	A,B,E,F,H	NO	-	YES
162-2 - Anaerobic Soil	TGAI or PAIRA	A	NO	-	YES
162-3 - Anaerobic Aquatic	TGAI or PAIRA			-	(4)
162-4 - Aerobic Aquatic	TGAI or PAIRA			-	(4)
MOBILITY STUDIES:					
163-1 - Leaching and Adsorption/Desorption	TGAI or PAIRA	A,B,E,F,H	NO	-	YES (5)
163-2 - Volatility (Lab)	TEP	A,E,F		-	(4)
163-3 - Volatility (Field)	TEP	A,E,F		-	(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-trans Allethrin (allyl homolog of cinerin I)
(Bioallethrin)

Data Requirement	Composition[1]	Use Pattern[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]
§158.130 Environmental Fate (continued)					
DISSIPATION STUDIES-FIELD:					
164-1 - Soil	TEP	A,B,H	NO	-	YES
164-2 - Aquatic (Sediment)	TEP			-	(4)
164-3 - Forestry	TEP			-	(4)
164-4 - Combination and Tank Mixes	TEP			-	(4)
164-5 - Soil, Long-term	TEP	A	NO	-	(6)
ACCUMULATION STUDIES:					
165-1 - Rotational Crops (Confined)	PAIRA	A	NO	-	YES
165-2 - Rotational Crops (Field)	TEP	A	NO	-	(7)
165-3 - Irrigated Crops	TEP			-	(8)
165-4 - In Fish	TGAI or PAIRA	A,B,D	NO	-	YES
165-5 - In Aquatic Nontarget Organisms	TEP				(8)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-trans Allethrin (allyl homolog of cinerin I)
(Bioallethrin)

Data Requirement	Composition[1]	Use Pattern[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]
§158.140 Reentry Protection					
132-1 - Foliar Dissipation	TEP	A,B	-	-	NO
132-1 - Soil Dissipation	TEP	A,B	-	-	NO
133-3 - Dermal Exposure	TEP	A,B	-	-	NO
133-4 - Inhalation Exposure	TEP	A,B	-	-	NO
§158.142 Spray Drift					
201-1 - Droplet Size Spectrum	TEP	A,B	-	-	NO
201-1 - Drift Field Evaluation	TEP	A,B	-	-	NO
§158.75 Other Exposure Data		-	-	-	NO (9)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-trans Allethrin (allyl homolog of cinerin I)
(Bioallethrin)

FOOTNOTES:

1/ Composition: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabelled; TEP = Typical end-use product; AEP=Applied end-use product.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor.

3/ Data must be submitted within the indicated timeframes, which begin on the date of the Guidance Document (see front cover for this date).

4/ Data are not required to support current registered uses or are otherwise not applicable for this standard.

5/ Adsorption/desorption(batch equilibrium)data are specifically needed to support the use on cranberries. Data are also needed to support all the other uses.

6/ Data may be required depending on the results of field dissipation studies on terrestrial food crops and aerobic soil metabolism studies.

7/ Data may be required if significant residues of concern are found in the confined rotational crop study.

8/ Data are required to support the use on cranberries.

9/ Available toxicology data indicate that no exposure data will be needed at this time.

TASKS 1 and 2

REGISTRATION STANDARD FOR THE BIOALLETHRIN GROUP

(2) Allethrin (allyl homolog of cinerin I)

EPA Shaughnessy Code 004001

INTRODUCTION

Allethrin (allyl homolog of cinerin I) is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial food crops (e.g. vegetables, citrus fruits and other orchard crops), terrestrial nonfood uses(e.g. ornamental plants and turf and recreational areas), aquatic nonfood uses(aquatic sites), greenhouse food crops(vegetables), greenhouse nonfood crops(e.g. ornamental plants), domestic outdoor(domestic dwellings) and indoor(postharvest use on fruits, vegetables and grains, stored foods and indoor plants and trees). Allethrin formulations almost always contain a synergist and one or more other active ingredients. End use formulations include dust (0.16%),impregnated materials (0.35-99.8%), EC (0.05-15%), SC/L (0.03-13.34%), RTU (0.019-1.39%), oil (0.162%), pressurized liquids (0.03-2.5%).

TASK I No data were available for review.

TASK II

EXECUTIVE SUMMARY No data were reviewed.

RECOMMENDATIONS

Available data are insufficient to fully assess the environmental fate and transport of, and the potential exposure of humans and nontarget organisms to allethrin (allyl homolog of cinerin I). A summary of registration requirements (Subdivision N) for terrestrial food crops, terrestrial nonfood, aquatic nonfood, greenhouse food crop, greenhouse nonfood, domestic outdoor and indoor use sites is given below:

Hydrolysis studies: No data were reviewed, but all data are required.

Photodegradation studies in water: No data were reviewed, but all data are required.

Photodegradation studies on soil: No data were reviewed, but all data are required.

Photodegradation studies in air: No data were reviewed, however no data are required.

Aerobic soil metabolism studies: No data were reviewed, but all data are required.

Anaerobic soil metabolism studies: No data were reviewed, but all data are required.

Aerobic aquatic metabolism studies: No data were reviewed, but all data are required.

Anaerobic aquatic metabolism studies: No data were reviewed, but all data are required.

Leaching and adsorption/desorption studies: No data were reviewed, but all data are required.

Laboratory volatility studies: No data were reviewed, however no data are required.

Field volatility studies: No data were reviewed, however no data are required.

Terrestrial field dissipation studies: No data were reviewed, but all data are required.

Aquatic field dissipation studies: No data were reviewed, but all data are required.

Forestry dissipation studies: No data were reviewed, no data are required because there are no forestry uses for the active ingredient.

Dissipation studies for combination products and tank mix uses: No data were reviewed; however, no data are required because data requirements for combination products and tank mix uses are currently not being imposed.

Long-term field dissipation studies: No data were reviewed, but all data may be required unless field residues reach 50% dissipation prior to recommended subsequent application to the same site, or if aerobic soil metabolism or aerobic aquatic metabolism studies indicate that residues are greater than 50% of initial application at the time of subsequent application.

Confined accumulation studies on rotational crops: No data were reviewed, but all data are required.

Field accumulation studies on rotational crops: No data were reviewed; however this data requirement is deferred pending evaluation of the results of the confined rotational crop study.

Accumulation studies on irrigated crops: No data were reviewed, data may be required if water from treated aquatic sites is used to irrigate crops.

Laboratory studies of pesticide accumulation in fish: No data were reviewed, but all data were required.

Field accumulation studies on aquatic nontarget organisms: No data were reviewed, but all data are required.

Reentry Studies

Under 40 CFR § 158.140, reentry data are required for Allethrin (allyl homolog of cinerin I) if the pesticide and its use patterns meet certain criteria. Those criteria include both toxicity and exposure. The "When required" paragraphs of Subdivision K discuss the circumstances under which § 158.140 requires reentry data. The toxicity criteria for requirement of a proposed reentry interval and supporting data, are as follows:

-The acute dermal toxicity of the technical grade of active ingredient is less than 200 mg/kg (body weight); or
-The acute inhalation toxicity of the technical grade of active ingredient is less than 200 mg/m^3 (for a one hour exposure); or
-The acute oral toxicity of the technical grade of active ingredient is less than 50 mg/kg (body weight); or
-Neurotoxic, teratogenic, or oncogenic effects or other adverse effects as evidenced by subchronic, chronic and reproduction studies would be expected from entry of persons into treated sites; or
-The Agency recieves other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects on persons entering treated sites.

These toxicity criteria are based on toxicities of the technical pesticide and its toxic alteration products. This is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

The exposure criteria are based on the pesticide's use types. The use type criteria for requirement of a proposed reentry interval and the supporting data are listed in 40 CFR § 158.140 and are discussed in ¶ 130-3 of Subdivision K. These use types are characterized by a high likelihood of dermal or inhalation exposure of persons who enter sites

included in these classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has become airborne.

Reentry data are required under 40 CFR § 158.140 only when both the toxicity and the exposure criteria are met. When reentry data are required, those data are to support the registration of the end-use product and each manufacturing-use product used to formulate each end-use product. Data will normally be gathered by the manufacturer of the manufacturing-use product but using an end-use product for the tests.

Allethrin (allyl homolog of cinerin I) does meet the exposure criteria of 40 CFR 158.140 in that it is used on crops where human exposure could occur, but available toxicology data do not indicate that it meets any of the toxicity criteria. However, if the results of the toxicology testing requirements indicate that bioallethrin does meet any of the toxicity criteria, reentry data will be required. No data are required at this time.

Spray drift studies: No data were reviewed, however no data are required.

GROUNDWATER No data are currently available to assess the potential for allethrin to contaminate groundwater.

LABEL REQUIREMENTS:

ROTATED CROPS: No rotational crop restriction is being imposed at this time since data are currently not available to form the basis of a restrictive interval. When the required data have been received and evaluated a label restriction may be imposed.

IRRIGATED CROPS: If water from treated aquatic sites is used to irrigate crops then irrigated crop data will be required. After receipt and evaluation of these data a label restriction on the use of this water may be imposed.

REFERENCES

The following study was not reviewed because it contains product chemistry data only:

Mitchell, L. 1961. The effect of ultraviolet light (2537 A) on 141 pesticide chemicals by paper chromatography. J. A.O.A.C. 44(4):643-651, 686, 712. (00158197)

The following study was not reviewed because it contains product chemistry data and a photodegradation on glass experiment only:

Miskus, R. and T. Andrews. 19??. Stabilization of thin films of pyrethrins and allethrin. Pyrethrum Post:135-136. Incomplete; also In unpublished submission received Jan. 21, 1977 under 6296-24; submitted by Nutrilite Products, Inc., Buena Park, CA; CDL:229731-B. (00113574)

The following study was not reviewed because it contains analytical methodology, a photodegradation on glass experiment, product chemistry, and directions for use only:

Sumitomo Chemical Co., Ltd. 1972. Chemical study--pynamin forte. Compilation; unpublished study received Nov. 26, 19[illegible] under 10308-3; CDL:026202-A. (00122922)

The following study (duplicate hardcopies received) was not reviewed because it contains bioassays, residue chemistry, and a photodegradation on glass experiment only:

Elliott, M., A.W. Farnham, N.F. Janes, et al. 1973. NRDC 143: A more stable pyrethroid. Pages 721-728, In Proceedings, 7th British Insecticide and Fungicide Conference. N.P. Also In unpublished submission received Feb. 3, 1977 under 10182-EX-7; submitted by ICI Americas, Inc., Wilmington, DE; CDL:228608-B. (0006649 and 00060035)

TABLE A
GENERIC DATA REQUIREMENTS FOR Allethrin (allyl homolog of cinerin I)

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFR/ § 3(c)(2)(B)? Time frames for Data Submission[3/]
§158.130 Environmental Fate					
DEGRADATION STUDIES-LAB:					
161-1 - Hydrolysis	TGAI or PAIRA	A,B,D,E,F,H	NO	-	YES
Photodegradation					
161-2 - In water	TGAI or PAIRA	A,B,D	NO	-	YES
161-3 - On soil	TGAI or PAIRA	A	NO	-	YES
161-4 - In Air	TGAI or PAIRA	A		-	(4)
METABOLISM STUDIES-LAB:					
162-1 - Aerobic Soil	TGAI or PAIRA	A,B,E,F,H	NO	-	YES
162-2 - Anaerobic Soil	TGAI or PAIRA	A	NO	-	YES
162-3 - Anaerobic Aquatic	TGAI or PAIRA	D	NO	-	YES
162-4 - Aerobic Aquatic	TGAI or PAIRA	D	NO	-	YES
MOBILITY STUDIES:					
163-1 - Leaching and Adsorption/Desorption	TGAI or PAIRA	A,B,D,E,F,H	NO	-	YES
163-2 - Volatility (Lab)	TEP	A,E,F		-	(4)
163-3 - Volatility (Field)	TEP	A,E,F		-	(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR Allethrin (allyl homolog of cinerin I)

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.130 Environmental Fate (continued)					
DISSIPATION STUDIES-FIELD:					
164-1 - Soil	TEP	A,B,H	NO	-	YES
164-2 - Aquatic (Sediment)	TEP	D	NO	-	YES
164-3 - Forestry	TEP			-	(4)
164-4 - Combination and Tank Mixes	TEP			-	(4)
164-5 - Soil, Long-term	TEP	A	NO	-	(5)
ACCUMULATION STUDIES:					
165-1 - Rotational Crops (Confined)	PAIRA	A	NO	-	YES
165-2 - Rotational Crops (Field)	TEP	A	NO	-	YES (6)
165-3 - Irrigated Crops	TEP	D	NO	-	YES (7)
165-4 - In Fish	TGAI or PAIRA	A,B,D	NO	-	YES
165-5 - In Aquatic Nontarget Organisms	TEP	D	NO	-	YES

TABLE A
GENERIC DATA REQUIREMENTS FOR Allethrin (allyl homolog of cinerin I)

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.140 Reentry Protection					
132-1 - Foliar Dissipation	TEP	A,B,D	-	-	NO
132-1 - Soil Dissipation	TEP	A,B,D	-	-	NO
133-3 - Dermal Exposure	TEP	A,B,D	-	-	NO
133-4 - Inhalation Exposure	TEP	A,B,D	-	-	NO
§158.142 Spray Drift					
201-1 - Droplet Size Spectrum	TEP	A,B,D		-	NO
201-1 - Drift Field Evaluation	TEP	A,B,D		-	NO
§158.75 Other Exposure Data		-		-	NO (8)

TABLE A
GENERIC DATA REQUIREMENTS FOR Allethrin(allyl homolog of cinerin I)

FOOTNOTES:

1/ Composition: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabelled; TEP = Typical end-use product; AEP=Applied end-use product.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor.

3/ Data must be submitted within the indicated timeframes, which begin on the date of the Guidance Document (see front cover for this date).

4/ Data are not required to support current registered uses or are otherwise not applicable for this standard.

5/ Data may be required depending on the results of field dissipation studies on [illegible] food crops and aerobic soil metabolism studies.

6/ Data may be required if significant residues of concern are found in the confined rotational crop study.

7/ Data are required if treated water is used for irrigation.

8/ Available toxicology data indicate that no exposure data will be needed at this time.

TASKS 1 and 2

REGISTRATION STANDARD FOR THE BIOALLETHRIN GROUP

(3) S-Bioallethrin(d-trans chrysanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one

EPA Shaughnessy Code 004004

INTRODUCTION

S-Bioallethrin(d-trans chrysanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one) is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial nonfood crops (ornamental plants), domestic outdoor(domestic dwellings,outdoor)and many domestic, commercial, industrial and institutional indoor uses. S-Bioallethrin formulations almost always contain a synergist and one or more other active ingredients. End use formulations include EC (0.319-2.973%), SC/L (0.93-1.39%), RTU (0.012-2.97%), pressurized liquid (0.025-0.197%).

TASK I No data were available for review.

TASK II

EXECUTIVE SUMMARY No data were reviewed.

RECOMMENDATIONS

Available data are insufficient to fully assess the environmental fate and transport of, and the potential exposure of humans and nontarget organisms to S-bioallethrin. A summary of registration requirements (Subdivision N) for terrestrial nonfood crop, domestic outdoor and indoor use sites is given below:

Hydrolysis studies: No data were reviewed, but all data are required.

Photodegradation studies in water: No data were reviewed, but all data are required.

Photodegradation studies on soil: No data were reviewed, however no data are required.

Photodegradation studies in air: No data were reviewed, however no data are required.

Aerobic soil metabolism studies: No data were reviewed, but all data are required.

Anaerobic soil metabolism studies: No data were reviewed, however no data are required.

Aerobic aquatic metabolism studies: No data were reviewed, however no data are required.

Anaerobic aquatic metabolisn studies: No data were reviewed, however no data are required.

Leaching and adsorption/desorption studies: No data were reviewed, but all data are required.

Laboratory volatility studies: No data were reviewed, however no data are required.

Field volatility studies: No data were reviewed, however no data are required

Terrestrial field dissipation studies: No data were reviewed, but all data are required.

Aquatic field dissipation studies: No data were reviewed, however no data are required.

Forestry dissipation studies: No data were reviewed, no data are required because there are no forestry uses for the active ingredient.

Dissipation studies for combination products and tank mix uses: No data were reviewed; however no data are required because data requirements for combination products and tank mix uses are currently not being imposed.

Long-term field dissipation studies: No data were reviewed, however no data are required.

Confined accumulation studies on rotational crops: No data were reviewed, however no data are required.

Field accumulation studies on rotational crops: No data were reviewed; however no data are required.

Accumulation studies on irrigated crops: No data were reviewed, however no data are required.

Laboratory studies of pesticide accumulation in fish: No data were reviewed, but all data were required.

Field accumulation studies on aquatic nontarget organisms: No data were reviewed, however no data are required.

Reentry Studies

Under 40 CFR § 158.140, reentry data are required for S-bioallethrin if the pesticide and its use patterns meet certain criteria. Those criteria include both toxicity and exposure. The "When required" paragraphs of Subdivision K discuss the circumstances under which § 158.140 requires reentry data. The toxicity criteria for requirement of a proposed reentry interval and supporting data, are as follows:

-The acute dermal toxicity of the technical grade of active ingredient is less than 200 mg/kg (body weight); or
-The acute inhalation toxicity of the technical grade of active ingredient is less than 200 mg/m^3 (for a one hour exposure); or
-The acute oral toxicity of the technical grade of active ingredient is less than 50 mg/kg (body weight); or
-Neurotoxic, teratogenic, or oncogenic effects or other adverse effects as evidenced by subchronic, chronic and reproduction studies would be expected from entry of persons into treated sites; or
-The Agency recieves other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects on persons entering treated sites.

These toxicity criteria are based on toxicities of the technical pesticide and its toxic alteration products. This is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

The exposure criteria are based on the pesticide's use types. The use type criteria for requirement of a proposed reentry interval and the supporting data are listed in 40 CFR § 158.140 and are discussed in § 130-3 of Subdivision K. These use types are characterized by a high likelihood of dermal or inhalation exposure of persons who enter sites included in these classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has become airborne.

Reentry data are required under 40 CFR §158.140 only when both the toxicity and the exposure criteria are met. When reentry data are required, those data are to support the registration of the end-use product and each manufacturing-use product used to formulate each end-use product. Data will normally be gathered by the manufacturer of the manufacturing-use product but using an end-use product for the tests.

S-bioallethrin does not meet the exposure criteria of 40 CFR §158.140 in that it is not used on crops where human exposure could occur, and available toxicology data do not indicate that it meets any of the toxicity criteria. No data are required.

Spray drift studies: No data were reviewed, however no data are required.

GROUNDWATER No data are currently available to assess the potential for S-bioallethrin to contaminate groundwater.

LABEL REQUIREMENTS None.

REFERENCES

The following study was not reviewed because it contains product chemistry data only:

Mitchell, L. 1961. The effect of ultraviolet light (2537 A) on 141 pesticide chemicals by paper chromatography. J. A.O.A.C. 44(4):643-651, 686,712. (00158197)

The following study was not reviewed because it contains product chemistry data and a photodegradation on glass experiment only:

Miskus, R. and T. Andrews. 19??. Stabilization of thin films of pyrethrins and allethrin. Pyrethrum Post:135-136. Incomplete; also In unpublished submission received Jan. 21, 1977 under 6296-24; submitted by Nutrilite Products, Inc., Buena Park, CA; CDL:229731-B. (00113574)

The following study was not reviewed because it contains analytical methodology a photodegradation on glass experiment, product chemistry, and directions for use only:

Sumitomo Chemical Co., Ltd. 1972. Chemical study--pynamin forte. Compilation unpublished study received Nov. 26, 1973 under 10308-3; CDL:026202-A. (00122922).

The following study (duplicate hardcopies received) was not reviewed because it contains bioassays, residue chemistry, and a photodegradation on glass experiment only:

Elliott, M., A.W. Farnham, N.F. Janes, et al. 1973. NRDC 143: A more stable pyrethroid. Pages 721-728, In Proceedings, 7th British Insecticide and Fungicide Conference. N.P. Also In unpublished submission received Feb.3, 1977 under 10182-EX-7; submitted by ICI Americas, Inc., Wilmington, DE; CDL:228608-B (00006649 and 00060035)

TABLE A
GENERIC DATA REQUIREMENTS FOR S-Bioallethrin

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.130 Environmental Fate					
DEGRADATION STUDIES-LAB:					
161-1 - Hydrolysis	TGAI or PAIRA	B,H	NO	-	YES
Photodegradation					
161-2 - In water	TGAI or PAIRA	B	NO	-	YES
161-3 - On soil	TGAI or PAIRA				(4)
161-4 - In Air	TGAI or PAIRA				(4)
METABOLISM STUDIES-LAB:					
162-1 - Aerobic Soil	TGAI or PAIRA	B,H	NO	-	YES
162-2 - Anaerobic Soil	TGAI or PAIRA				(4)
162-3 - Anaerobic Aquatic	TGAI or PAIRA				(4)
162-4 - Aerobic Aquatic	TGAI or PAIRA				(4)
MOBILITY STUDIES:					
163-1 - Leaching and Adsorption/Desorption	TGAI or PAIRA	B,H	NO	-	YES
163-2 - Volatility (Lab)	TEP				(4)
163-3 - Volatility (Field)	TEP				(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR S-Bioallethrin

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.130 Environmental Fate (continued)					
DISSIPATION STUDIES-FIELD:					
164-1 - Soil	TEP	B,H	NO	-	YES (4)
164-2 - Aquatic (Sediment)	TEP				(4)
164-3 - Forestry	TEP				(4)
164-4 - Combination and Tank Mixes	TEP				(4)
164-5 - Soil, Long-term	TEP				(4)
ACCUMULATION STUDIES:					
165-1 - Rotational Crops (Confined)	PAIRA				(4)
165-2 - Rotational Crops (Field)	TEP				(4)
165-3 - Irrigated Crops	TEP				(4)
165-4 - In Fish	TGAI or PAIRA	B	NO	-	YES (4)
165-5 - In Aquatic Nontarget Organisms	TEP				(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR S-Bioallethrin

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.140 Reentry Protection					
132-1 - Foliar Dissipation	TEP	B	-	-	NO
132-1 - Soil Dissipation	TEP	B	-	-	NO
133-3 - Dermal Exposure	TEP	B	-	-	NO
133-4 - Inhalation Exposure	TEP	B	-	-	NO
§158.142 Spray Drift					
201-1 - Droplet Size Spectrum	TEP	B	-	-	NO
201-1 - Drift Field Evaluation	TEP	B	-	-	NO
§158.75 Other Exposure Data		-	-	-	NO (5)

TABLE A
GENERIC DATA REQUIREMENTS FOR S-Bioallethrin

FOOTNOTES:

1/ Composition: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabelled; TEP = Typical end-use product; AEP=Applied end-use product.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor.

3/ Data must be submitted within the indicated timeframes, which begin on the date of the Guidance Document (see front cover for this date).

4/ Data are not required to support current registered uses or are otherwise not applicable for this standard.

5/ Available toxicology data indicate that no exposure data will be needed at this time.

TASKS 1 and 2

REGISTRATION STANDARD FOR THE BIOALLETHRIN GROUP

(4) d-cis/trand allethrin

EPA Shaughnessy Code 004005

INTRODUCTION

D-cis/trans allethrin is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes and bees. It is registered for use on terrestrial nonfood crops(e.g. ornamental plants and forest trees) and for indoor uses (e.g. ornamental plants and domestic, commercial and industrial uses). D-cis/trans allethrin formulations almost always contain a synergist and/or one or more other active ingredients. End use formulations include impregnated materials (0.23-21.65%), EC (3.12%), SC/L (0.31%) and pressurized liquids (0.13-0.5%).

TASK I No data available for review.

TASK II

EXECUTIVE SUMMARY No data were reviewed.

RECOMMENDATIONS

Available data are insufficient to fully assess the environmental fate and transport of, and the potential exposure of humans and nontarget organisms to d-cis/trans allethrin. A summary of registration requirements (Subdivision N) for terrestrial nonfood and indoor uses is given below:

Hydrolysis studies: No data were reviewed, but all data are required.

Photodegradation studies in water: No data were reviewed, but all data are required.

Photodegradation studies on soil: No data were reviewed, however no data are required.

Photodegradation studies in air: No data were reviewed, however no data are required.

Aerobic soil metabolism studies: No data were reviewed, but all data are required.

Anaerobic soil metabolism studies: No data were reviewed, however no data are required.

Aerobic aquatic metabolism studies: No data were reviewed, however no data are required.

Anaerobic aquatic metabolism studies: No data were reviewed, however no data are required.

Leaching and adsorption/desorption studies: No data were reviewed, but all data are required.

Laboratory volatility studies: No data were reviewed, however no data are required.

Field volatility studies: No data were reviewed, however no data are re-required.

Terrestrial field dissipation studies: No data were reviewed, but all data are required.

Aquatic field dissipation studies: No data were reviewed, however no data are required.

Forestry dissipation studies: No data were reviewed, however no data are required.

Dissipation studies for combination products and tank mix uses: No data were reviewed; however no data are required because data requirements for combination products and tank mix uses are currently not being imposed.

Long-term field dissipation studies: No data were reviewed, however no data were required

Confined accumulation studies on rotational crops: No data were reviewed, however no data are required.

Field accumulation studies on rotational crops: No data were reviewed; however no data are required.

Accumulation studies on irrigated crops: No data were reviewed, however no data are required.

Laboratory studies of pesticide accumulation in fish: No data were reviewed, but all data were required.

Field accumulation studies on aquatic nontarget organisms: No data were reviewed, howver no data are required.

Reentry Studies

Under 40 CFR § 158.140, reentry data are required for d-cis/trans allethrin if the pesticide and its use patterns meet certain criteria. Those criteria include both toxicity and exposure. The "When required" paragraphs of Subdivision K discuss the circumstances under which § 158.140 requires reentry data.

The toxicity criteria for requirement of a proposed reentry interval and supporting data, are as follows:

-The acute dermal toxicity of the technical grade of active ingredient is less than 200 mg/kg (body weight); or
-The acute inhalation toxicity of the technical grade of active ingredient is less than 200 mg/m^3 (for a one hour exposure); or
-The acute oral toxicity of the technical grade of active ingredient is less than 50 mg/kg (body weight); or
-Neurotoxic, teratogenic, or oncogenic effects or other adverse effects as evidenced by subchronic, chronic and reproduction studies would be expected from entry of persons into treated sites; or
-The Agency recieves other scientifically validated toxicological or epidemiological evidence that a pesticide or residue of a pesticide could cause adverse effects on persons entering treated sites.

These toxicity criteria are based on toxicities of the technical pesticide and its toxic alteration products. This is necessary because persons reentering treated sites will normally not be exposed to the formulated product or to its diluted form as applied, but rather to a "weathered" or environmentally modified and dissipated residue, which no longer is composed of the same mixture or ratio of components present in the formulated product.

The exposure criteria are based on the pesticide's use types. The use type criteria for requirement of a proposed reentry interval and the supporting data are listed in 40 CFR § 158.140 and are discussed in §130-3 of Subdivision K. These use types are characterized by a high likelihood of dermal or inhalation exposure of persons who enter sites included in these classes. Dermal exposure will generally arise from contact with treated foliar, fruit, or soil surfaces; inhalation exposure will normally arise from respiration of volatilized pesticide residues and residues adhering to particulate matter which has become airborne.

Reentry data are required under 40 CFR § 158.140 only when both the toxicity and the exposure criteria are met. When reentry data are required, those data are to support the registration of the end-use product and each manufacturing-use product used to formulate each end-use product. Data will normally be gathered by the manufacturer of the manufacturing-use product but using an end-use product for the tests.

D-cis/trans allethrin does not meet the exposure criteria of 40 CFR 158.140 in that it is not used on crops where human exposure could occur, and available toxicology data do not indicate that it meets any of the toxicity criteria. No data are required.

Spray drift studies: No data were reviewed, however no data are required.

GROUNDWATER No data are currently available to assess the potential for d-cis/trans allethrin to contaminate groundwater.

LABEL REQUIREMENTS: None

REFERENCES

The following study was not reviewed because it contains product chemistry data only:

Mitchell, L. 1961. The effect of ultraviolet light (2537 A) on 141 pesticide chemicals by paper chromatography. J. A.O.A.C. 44(4):643-651, 686, 712. (00158197)

The following study was not reviewed because it contains product chemistry data and a photodegradation on glass experiment only:

Miskus, R. and T. Andrews. 19??. Stabilization of thin films of pyrethrins and allethrin. Pyrethrum Post:135-136. Incomplete; also In unpublished submission received Jan. 21, 1977 under 6296-24; submitted by Nutrilite Products, Inc., Buena Park, CA; CDL:229731-B. (00113574)

The following study was not reviewed because it contains analytical methodology, a photodegradation on glass experiment, product chemistry, and directions for use only:

Sumitomo Chemical Co., Ltd. 1972. Chemical study--pynamin forte. Compilation unpublished study received Nov. 26, 1973 under 10308-3; CDL:026202-A. (00122922)

The following study (duplicate hardcopies received) was not reviewed because it contains bioassays, residue chemistry, and a photodegradation on glass experiment only:

Elliott, M., A.W. Farnham, N.F. Janes, et al. 1973. NRDC 143: A more stable pyrethroid. Pages 721-728, In Proceedings, 7th British Insecticide and Fungicide Conference. N.P. Also In unpublished submission received Feb. 3, 1977 under 10182-EX-7; submitted by ICI Americas, Inc., Wilmington, DE; CDL:228608-B (0006649 and 00060035)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-cis/trans Allethrin

Data Requirement	Composition[1]	Use Pattern[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3]
§158.130 Environmental Fate					
DEGRADATION STUDIES-LAB:					
161-1 - Hydrolysis	TGAI or PAIRA	B	NO	-	YES
Photodegradation					
161-2 - In water	TGAI or PAIRA	B	NO	-	YES
161-3 - On soil	TGAI or PAIRA				(4)
161-4 - In Air	TGAI or PAIRA				(4)
METABOLISM STUDIES-LAB:					
162-1 - Aerobic Soil	TGAI or PAIRA	B	NO	-	YES
162-2 - Anaerobic Soil	TGAI or PAIRA				(4)
162-3 - Anaerobic Aquatic	TGAI or PAIRA				(4)
162-4 - Aerobic Aquatic	TGAI or PAIRA				(4)
MOBILITY STUDIES:					
163-1 - Leaching and Adsorption/Desorption	TGAI or PAIRA	B	NO	-	YES
163-2 - Volatility (Lab)	TEP				(4)
163-3 - Volatility (Field)	TEP				(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-cis/trans Allethrin

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.130 Environmental Fate (continued)					
DISSIPATION STUDIES-FIELD:					
164-1 - Soil	TEP	B	NO	–	YES
164-2 - Aquatic (Sediment)	TEP				(4)
164-3 - Forestry	TEP				(4)
164-4 - Combination and Tank Mixes	TEP				(4)
164-5 - Soil, Long-term	TEP				(4)
ACCUMULATION STUDIES:					
165-1 - Rotational Crops (Confined)	PAIRA				(4)
165-2 - Rotational Crops (Field)	TEP				(4)
165-3 - Irrigated Crops	TEP				(4)
165-4 - In Fish	TGAI or PAIRA	B	NO	-	YES
165-5 - In Aquatic Nontarget Organisms	TEP				(4)

TABLE A
GENERIC DATA REQUIREMENTS FOR d-cis/trans-Allethrin

Data Requirement	Composition[1/]	Use Pattern[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B)? Timeframes for Data Submission[3/]
§158.140 Reentry Protection					
132-1 - Foliar Dissipation	TEP	B	-	-	NO
132-1 - Soil Dissipation	TEP	B	-	-	NO
133-3 - Dermal Exposure	TEP	B	-	-	NO
133-4 - Inhalation Exposure	TEP	B	-	-	NO
§158.142 Spray Drift					
201-1 - Droplet Size Spectrum	TEP	B		-	NO
201-1 - Drift Field Evaluation	TEP	B		-	NO
§158.75 Other Exposure Data			-	-	NO (5)

TABLE A

GENERIC DATA REQUIREMENTS FOR d-cis/trans Allethrin

FOOTNOTES:

1/ Composition: TGAI = Technical grade of the active ingredient; PAIRA = Pure active ingredient, radiolabelled; TEP = Typical end-use product; AEP=Applied end-use product.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor.

3/ Data must be submitted within the indicated timeframes, which begin on the date of the Guidance Document (see front cover for this date).

4/ Data are not required to support current registered uses or are otherwise not applicable for this standard.

5/ Available toxicology data indicate that no exposure data are needed at this time.

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

JUL 22 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Exposure Assessment Branch Science Chapter
Bioallethrin Group Registration Standard

FROM: Emil Regelman, Supervisory Chemist
Exposure Assessment Branch, HED (TS-769c)

TO: Arturo E. Castillo, Product Manager #17
Insecticide Branch, RD (TS-769C)

THRU: Steve Johnson, Acting Chief
Exposure Assessment Branch, HED (TS-769c)

Attached are the EAB Task 1 and 2, and Table A (Generic Data Requirements) for the pesticide chemicals: Allethrin, d-trans Allethrin, Bioallethrin and S-Bioallethrin. This document supercedes the EAB Science Chapter of 5/14/87.

HED has concluded that EAB data requirements will be imposed for all of the use patterns noted, following a two tiered approach. Tier I would require preliminary evaluation of the persistence of two of the eight optical isomers found in the above-noted mixtures:

- o D-trans chrysanthemic acid of D-allethrolone
- o D-trans chrysanthemic acid of L-allethrolone

EAB has agreed to defer Tier II testing until evaluation of all data submitted under Tier one. Specific requirements could range from minimal to the full battery of laboratory and field testing, and might include testing not now being imposed.

It is strongly recommended that protocols be submitted for approval prior to initiation of testing. Protocols must include definitive discussions of analytical methodology to be used to quantitate parent and major degradates.

Attachment:

cc: Art Schlosser
Amy Rispin

INTRODUCTION

Allethrin (allyl homolog of cinerin I) is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial food crops (e.g. vegetables, citrus fruits and other orchard crops), terrestrial nonfood uses (e.g. ornamental plants and turf and recreational areas), aquatic nonfood uses (aquatic sites), greenhouse food crops (vegetables), greenhouse nonfood crops (e.g. ornamental plants), domestic outdoor (domestic dwellings) and indoor (postharvest use on fruits, vegetables and grains, stored foods and indoor plants and trees). Allethrin formulations almost always contain a synergist and one or more other active ingredients. End use formulations include dust (0.16%), impregnated materials (0.35-99.8%), EC (0.05-15%), SC/L (0.03-13.34%), RTU (0.019-1.39%), oil (0.162%), pressurized liquids (0.03-2.5%).

Bioallethrin [d-trans allethrin (allyl homolog of cinerin I)] is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial food crops (e.g. asparagus, beans, corn, tomatoes and non-bearing cranberries and citrus fruits), terrestrial nonfood crops (e.g. ornamental plants and forest trees), greenhouse food crops (e.g. asparagus, beans, corn, peppers and tomatoes), greenhouse nonfood crops (e.g. ornamental plants), domestic outdoor (domestic dwellings, outdoor) and many domestic, commercial and industrial indoor uses. Bioallethrin formulations almost always contain a synergist and one or more other active ingredients. End use formulations include dusts (0.15-1.8%), impregnated materials (0.125-4.8%), EC (0.837-6%), SC/L (0.06% - 0.324%), RTU (0.05-0.6%) and pressurize liquids (0.03-1.2%).

S-Bioallethrin (d-trans chrysanthemum monocarboxylic acid ester of d-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one) is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide and acaricide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes, lice, fleas and ticks. It is registered for use on terrestrial nonfood crops. (ornamental plants), domestic outdoor (domestic dwellings, outdoor) and many domestic, commercial, industrial and institutional indoor uses. S-Bioallethrin formulations almost always contain a synergist and one or more other active ingredients. Ends use formulations include EC (0.319-2.973%), SC/L (0.93-1.39%), RTU (0.012-2.97%), pressurized liquid (0.025-0.197%).

D-cis/trans allethrin is one of a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-ally-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of 2,2 dimethyl-1-(2-methyl propenyl) cyclopropane carboxylic acid. It is a broad spectrum insecticide used for control of a wide variety of pests including cockroaches, ants, flies, mosquitoes and bees. It is registered for use of terrestrial nonfood crops (e.g. ornamental plants and forest trees) and for indoor uses (e.g. ornamental plants) and domestic, commercial and industrial uses. D-cis/trans allethrin formulation almost always contain a synergist and/or one or more other active ingredients. Ends use formulations include impregnated materials (0.23-21.65%), EC (3.12%), SC/L (0.31%) and pressurized liquids (0.13-0.5%).

TASK I No data available for review.

TASK II

EXECUTIVE SUMMARY No data available to summarize.

RECOMMENDATIONS

Available data are insufficient to fully assess the environmental fate and transport of, and potential exposure of humans and nontarget organisms to allethrin, bioallethrin, S-bioallethrin or d-cis/trans allethrin.

HED has concluded that EAB data requirements will be imposed for all of the use patterns noted below, following a two tiered approach. Tier one would require preliminary evaluation of the persistence of two of the eight optical isomers found in the above-noted mixtures:

- o D-trans chrysanthemic acid of D-allethrolone
- o D-trans chrysanthemic acid of L-allethrolone

Tier two testing would be deferred until evaluation of all data submitted under tier one. Specific requirements could range from minimal to the full battery of laboratory and field testing, and might include testing not now being imposed.

The rationale for this approach is as follows:

1. In the team meeting of 7/7/87, it was reported that photodegradation of allethrins on soil and in water (to either CO_2 or residues of no toxicological concern) was likely to be extremely rapid (1-2 days). If this is found to be true, there will be very limited opportunity for uptake of residues of concern by crops/fish/non-target organisms, or for mobility through soil.

2. If degradation is as rapid as anticipated, EAB does not anticipate significant differences in the mode of degradation among the eight known isomers. Therefore, the two compounds selected should adequately represent the six.

3. If the allethrins are determined to be more than minimally persistent, then appropriate tier two testing will be required, based on the 'pilot' testing of tier one. This approach does not impose an unreasonable amount of early testing, but may lead to extensive data requirements for all isomers later on.

A summary of registration requirements (Subdivision N) for terrestrial food crops, terrestrial nonfood, aquatic nonfood, greenhouse food crop, greenhouse nonfood, domestic outdoor and indoor use sites is given below. These studies must be conducted individually on both D-trans chrysanthemic acid of D-allethrolone and D-trans chrysanthemic acid of L-allethrolone. Appropriate radiolabelling of analytical grade compounds is preferred.

It is strongly recommended that protocols be submitted for approval prior to initiation of testing. Protocol must include definitive discussions of analytical methodology to be used to quantitate parent and major degradates.

Data must be submitted under tier I to support the following ten subpart N requirements:

- o Hydrolysis (161-1)
- o Photodegradation in Water (161-2)
- o Photodegradation on Soil (161-3)
- o Photodegradation in Air (161-4)
- o Aerobic Soil Metabolism (162-1)
- o Anaerobic Soil Metabolism (162-2)
- o Aerobic Aquatic Metabolism (162-4)
- o (Unaged) leaching (column) (163-1)
- o Aged Leaching (column) (163-1)
- o Laboratory Volatility (163-2)

REENTRY: No data will be required under Tier I.

SPRAY DRIFT: No data will be required under Tier I.

GROUNDWATER: No data are currently available to assess the potential for allethrin to contaminate groundwater.

LABEL REQUIREMENTS:

ROTATED CROPS: No rotational crop restriction is being imposed at this time since data are currently not available to form the basis of a restrictive interval. When the required data have been received and evaluated a label restriction may be imposed.

IRRIGATED CROPS: If water from treated aquatic sites is used to irrigate crops then irrigated crop data will be required. After receipt and evaluation of these data a label restriction on the use of this water may be imposed.

REFERENCES:

The following study was not reviewed because it contains product chemistry data only:

Mitchell, L. 1961. The effect of ultraviolet light (2537 A) on 141 pesticide chemicals by paper chromatography. J. A.O.A.C. 44(4):643-651, 686, 712. (00158197)

The following study was not reviewed because it contains product chemistry data and a photodegradation on glass experiment only:

Miskus, R. and T. Andrews. 19??. Stabilization of thin films of pyrethrins and allethrin. Pyrethrum Post:135-136. Incomplete; also In unpublished submission received Jan. 21, 1977 under 6296-24; submitted by Nutrilite products, Inc., Buena Park, CA; CDL:229731-B. (00113574)

The following study was not reviewed because it contains analytical methodology, a photodegradation on glass experiment, product chemistry, and directions for use only:

Sumitomo Chemical., Ltd. 1972. Chemical study--pynamin forte. Compilation; unpublished study received Nov. 26, 1973 under 10308-3; CDL:026202-A. (00122922)

The following study (duplicate hardcopies received) was not reviewed because it contains bioassays, residue chemistry, and a photodegradation on glass experiment only:

Elliott, M., A.W. Farnham, N.F. Janes, et al. 1973. NRDC 143: A more stable pyrethroid. Page 721-728, In Proceedings, 7th British Insecticide and Fungicide Conference. N.P. Also In unpublished submission received Feb. 3, 1977 under 10182-EX-7; submitted by ICI Americas, Inc,. Wilmington, DE; CDL:228608-B: (0006649) and 00060035)

TABLE A

GENERIC DATA REQUIREMENTS FOR ALLETHRINS--Tier I Testing 1,2,3/

Data Requirement	Composition4/	Use Pattern5/	Does EPA have data to satisfy this requirement (Y/N/P) ?	Must additional data be submitted under FIFRA §3(c)(2)(b)? time frames for data submission?
§158.130 Environmental Fate				
DEGRADATION STUDIES-LAB:				
161-1 - Hydrolysis	PAIRA	A,B,D,E,F,H	NO	YES
Photodegradation				
161-2 - In water	PAIRA	A,B,D	NO	YES
161-3 - On Soil	PAIRA	A	NO	YES
161-4 - In Air	PAIRA	A,E,F,I	NO	YES
METABOLISM STUDIES-LAB:				
162-1 - Aerobic Soil	PAIRA	A,B,E,F,H	NO	YES
162-2 - Anaerobic Soil	PAIRA	A,B,E,F,H	NO	YES
162-4 - Aerobic Aquatic	PAIRA	D	NO	YES
MOBILITY STUDIES:				
163-1 - Leaching Aged Leaching	PAIRA	A,B,D,E,F,H	NO	YES
163-2 - Volatility (Lab)	PAIRA	A,E,F,I	NO	YES

1/ Only data noted in this table are being required under Tier I to support §158.130 requirements.

2/ No data requirements for either §158.140 (Reentry Protection) or §158.142 (Spray Drift) are being imposed for Tier I of this Standard.

3/ Additional data requirements may be imposed for Tier II based on the results of Tier I testing.

4/ PAIRA = Pure Active Ingredient, Radiolabelled (both D-trans chrysanthemic acid of D-allethrolone and D-trans chrysanthemic acid of L-allethrolone must be tested)

5/ A=Terrestrial Food Crop, B=Terrestrial Non-Food, D=Aquatic Non-Food, E=Greenhouse Food Crop, F=Greenhouse Non-Food, H=Domestic Outdoor, I=Domestic Indoor.

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

MAY 13 1987

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Bioallethrin Registration Standard

FROM: Zigfridas Vaituzis, Microbiologist
Ecological Effects Branch
Hazard Evaluation Division (TS-769C)

THRU: Harry T. Craven, Head, Section IV
Ecological Effects Branch
Hazard Evaluation Division (TS-769C)

THRU: Michael W. Slimak, Chief
Ecological Effects Branch
Hazard Evaluation Division (TS-769C)

TO: Richard King, PM Team 17
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

Attached are the Science Chapter and Generic Data Tables for the Ecological Effects portion of the Allethrin, Bioallethrin, s-Bioallethrin, and D-cis/trans-allethrin Registration Standard. The Data Evaluation Records will follow at a later date.

Attachment

cc: J. Heckman, MSS
A. Rispin, SIS

I. ECOLOGICAL EFFECTS

Topical Summary

Because the four registered chemicals - allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin - all contain the most biologically active stereoisomer (D-trans of D-isomer) as the major component, nontarget effects data on any one of the above were used to assess hazard of all four compounds (see Section II.B.1).

A. Effects on Birds

Four studies under four citations were reviewed by EEB. All were acceptable for hazard evaluation.

Author(s)	Date	MRID Number
Hudson, Tucker, Haegle	1984	HOOSTA01
Fink, Beavers, Grimes	1978	123339
Beavers, Fink, Brown	1978	027548
Beavers, Fink, Brown	1978	027547

The minimum data required to evaluate the hazard of allethrin, bioallethrin, s-bioallethrin and D-cis/trans-allethrin to birds are:

1. An avian single dose oral LD_{50} test with the technical grade of the active ingredient utilizing either one species of waterfowl, preferably the mallard duck, or one species of upland game bird, preferably the bobwhite quail; and

2. Two avian dietary LC_{50} tests with the technical grade of the active ingredient utilizing one species of waterfowl, preferably the mallard duck, and one species of upland game bird, preferably the bobwhite quail.

1. Avian Single-Dose Oral LD_{50} - Technical Grade

The avian single dose oral studies that are suitable for assessing the hazard of allethrin, bioallethrin, s-bioallethrin and D-cis/trans-allethrin are listed below.

Species	% ai	LD_{50} (mg/kg)	Authors	Date	MRID No.	Toxicity	Fulfills Guideline Requirements
Mallard duck (allethrin)	90%	> 2000	Hudson, Tucker, Haegle	1984	HOOSTA01	Practically nontoxic	Yes

These data indicate that technical allethrin is practically nontoxic to waterfowl species on an acute oral basis. The Guideline requirement for an avian acute oral study is fulfilled.

2. Avian Dietary LC_{50} - Technical

The avian dietary studies that are suitable for assessing the hazard of allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin are listed below.

Species	% ai	LC_{50} (ppm)	Author	Date	MRID Number	Toxicity	Fulfills Guideline Requirements
Bobwhite quail (Bioallethrin)	93.1%	2030	Fink, Beavers, Grimes	1978	123339	Slightly toxic	Yes
Mallard duck (D-cis/trans-allethrin)	93.4%	> 5620	Beavers, Fink, Brown	1978	027548	Practically nontoxic	Yes
Bobwhite quail (D-cis/trans-allethrin)	93.4%	> 5620	Beavers, Fink, Brown,	1978	027547	Practically nontoxic	Yes

These data indicate that technical bioallethrin and D-cis/trans-allethrin are practically nontoxic to avian species on a subacute basis.

B. Effects on Freshwater Fish

Twenty-seven studies under two citations were reviewed by EEB. All were acceptable for hazard evaluation.

Author	Date	MRID Number
Johnson, Finley	1980	003503
Mauck, Olson, Marking	1976	122546

The minimum data required to evaluate the hazard of allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin to freshwater fish are:

1. Two 96-hour freshwater fish toxicity tests. One test should utilize a coldwater species, preferrably the rainbow trout, and the other should utilize a warmwater species, preferably the bluegill sunfish.

2. When direct exposure of aquatic organisms to a chemical is expected, the formulated product testing is required.

1. Freshwater Fish LC_{50} - Technical

The studies that are suitable for evaluation of hazard to freshwater fish from technical grade allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin are listed below.

Chemical Species	% ai	96-Hour LC_{50} (ppb)	Author	Date	MRID Number	Toxicity	Fulfills Guideline Requirements
Allethrin							
Rainbow trout	90%	19	Johnson, Finley	1980	003503	Very highly toxic	Yes
Bluegill sunfish	90%	56	Johnson, Finley	1980	003503	Very highly toxic	Yes
s-Bioallethrin							
Fathead minnow	98%	80	Johnson, Finley	1980	003503	Very highly toxic	Yes
Channel catfish	98%	15	Johnson, Finley	1980	003503	Very highly toxic	Yes

Chemical Species	% ai	96-Hour LC_{50} (ppb)	Author	Date	MRID Number	Toxicity	Fulfills Guideline Requirements
s-Bioallethrin (cont'd)							
Bluegill sunfish	98%	24	Johnson, Finley	1980	003503	Very highly toxic	Yes
Yellow perch	98%	7.8	Johnson, Finley	1980	003503	Very highly toxic	No
Fathead minnow	98%	53.0	Mauck, Olson, Marking	1976	122546	Very highly toxic	No
Channel catfish	98%	14.6	Mauck, Olson, Marking	1976	122546	Very highly toxic	Yes
Yellow perch	98%	7.8	Mauck, Olson, Marking	1976	122546	Very highly toxic	No
Bluegill sunfish	98%	27.6-36.0	Mauck, Olson, Marking	1976	122546	Very highly toxic	Yes
Bioallethrin							
Coho salmon	90%	2.6	Johnson, Finley	1980	003503	Very highly toxic	Yes
Steelhead trout	90%	9.7	Johnson, Finley	1980	003503	Very highly toxic	No
Rainbow trout	90%	13.9	Johnson, Finley	1980	003503	Very highly toxic	Yes
Lake trout	90%	16.0	Johnson, Finley	1980	003503	Very highly toxic	No
Northern pike	90%	3.3	Johnson, Finley	1980	003503	Very highly toxic	No

Chemical Species	% ai	96-Hour LC_{50} (ppb)	Author	Date	MRID Number	Toxicity	Fulfills Guideline Requirements
Bioallethrin (cont'd)							
Fathead minnow	90%	48.0	Johnson, Finley	1980	003503	Very highly toxic	Yes
White sucker	90%	12.4	Johnson, Finley	1980	003503	Very highly toxic	No
Channel catfish	90%	> 30.0	Johnson, Finley	1980	003503	--	No
Bluegill sunfish	90%	22.5	Johnson, Finley	1980	003503	Very highly toxic	Yes
Smallmouth bass	90%	7.7	Johnson, Finley	1980	003503	Very highly toxic	No
Largemouth bass	90%	> 12.0	Johnson, Finley	1980	003503	--	No
Yellow perch	90%	9.9	Johnson, Finley	1980	003503	Very highly toxic	No
Coho salmon	90%	9.4	Mauck, Olson, Marking	1976	122546	Very highly toxic	Yes
Steelhead trout	90%	9.7	Mauck, Olson, Marking	1976	122546	Very highly toxic	No
Channel catfish	90%	27.0	Mauck, Olson, Marking	1976	122546	Very highly toxic	Yes
Yellow perch	90%	9.9	Mauck, Olson, Marking	1976	122546	Very highly toxic	No
Bluegill sunfish	90%	35-60	Mauck, Olson, Marking	1976	122546	Very highly toxic	Yes

The above data indicate that technical allethrin, s-bioallethrin, and bioallethrin are very highly toxic to both coldwater and warmwater fish species. The Guideline requirement for acute toxicity testing of the technical material on freshwater fish is fulfilled.

2. Freshwater Fish LC_{50} - Formulated Product

Testing of the multiple active ingredient formulated products is required when the pesticide will be introduced directly into an aquatic environment. There are no studies submitted under this Guideline. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

3. Fish Early Life Stage Testing

Data from fish early life stage tests are required when aquatic acute LD_{50} values are below 1 mg/L if the product is applied directly to water, or is expected to be transported to water from an intended use site.

The registered uses falling in this category are terrestrial and aquatic food and nonfood and forestry. There were no studies submitted under this Guideline. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

4. Fish Life Cycle Studies

Data are required if an end-use product is intended to be applied directly to water or is expected to transport to water from the intended use site or if the estimated environmental concentration is equal to or greater than 1/10 of the no-effect level in the fish early life stage test. The registered uses falling in this category are terrestrial and aquatic food and nonfood and forestry. There were no studies submitted under this Guideline. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

5. Simulated or Actual Field Testing

Testing is required on a case-by-case basis depending on the results of lower tier studies such as acute toxicity testing, intended use pattern, and pertinent environmental fate characteristics. Since the acute aquatic toxicity testing shows a very highly toxic nature of the chemicals, these studies are warranted for registered uses other than indoor, greenhouse and domestic outdoor.

Depending on environmental fate information, which was not available at the time this Standard was prepared, it is likely that aquatic field studies would be required when EEB has full access to use information through the Qualitative Use Assessment. It is also likely that these field studies would have to address the multiple active ingredient formulations to determine synergistic or additive effects. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

C. Effects on Freshwater Aquatic Invertebrates

Four studies under one citation were reviewed by EEB. All were acceptable for hazard evaluation.

Authors	Date	MRID Number
Johnson & Finley	1980	003503

The minimum data required to assess the hazard of allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin to freshwater aquatic invertebrates is a 48-hour acute study, using the technical grade of the active ingredient, on first instar Daphnia magna or early instar amphipods, stoneflies, or mayflies.

When there is expected to be direct exposure of aquatic organisms to a chemical, formulated product testing is required. The registered uses falling in this category are terrestrial and aquatic food and nonfood and forestry.

1. Invertebrate Acute LC_{50} - Technical

The studies that are suitable for evaluation of hazard to freshwater aquatic invertebrates from technical grade allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin are listed below.

Chemical, Species	% ai	LC_{50} (ppb)	Author	Date	MRID No.	Toxicity	Fulfills Guideline Requirements
Allethrin							
Simoncephalus (blackfly)	90%	56.0 (48 h)	Johnson, Finley	1980	003503	Very highly toxicity	No
Daphnia pulex	90%	21.0 (48 h)	Johnson, Finley	1980	003503	Very highly toxicity	Yes
G.fasciatus (amphipod)	90%	11.0 (96 h)	Johnson, Finley	1980	003503	Very highly toxicity	Yes
Pteronarcys (stonefly)	90%	5.6 (96 h)	Johnson, Finley	1980	003503	Very highly toxicity	Yes

The above data indicate that technical allethrin is very highly toxic to freshwater aquatic invertebrates. The Guidelines requirement for acute toxicity testing of the technical material on freshwater aquatic invertebrates is fulfilled.

2. Invertebrate Acute LC_{50} - Formulated Product

Testing of the multiple active ingredient formulated products is required when the pesticide will be introduced directly into an aquatic environment. There are no studies submitted under this Guideline. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

3. Aquatic Invertebrate Life Cycle Test

Data from an aquatic invertebrate life cycle test are required when aquatic acute LD_{50} values are below 1 mg/L if the product is applied directly to water, or is expected to be transported to water from an intended use site.

The registered uses falling in this category are terrestrial and aquatic food and nonfood and forestry. There were no studies submitted under this Guideline. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

4. Simulated or Actual Field Testing

Testing is required on a case-by-case basis depending on the results of lower tier studies such as acute toxicity category, intended use pattern, and pertinent environmental fate characteristics. Since the acute aquatic toxicity testing shows a very highly toxic nature of the chemicals, these studies are warranted for registered uses other than indoor, greenhouse and domestic outdoor.

Depending on environmental fate information, which was not available at the time this Standard was prepared, it is likely that aquatic field studies would be required when EEB as full access to use information through the Qualitative Use Assessment. It is also likely that these field studies would have to address the multiple active ingredient formulations to determine synergistic or additive effects. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

D. Effects on Estuarine and Marine Organisms

1. The minimum data required to assess the hazard to estuarine and marine organisms are:

a) a 96-hour LC_{50} for the sheepshead minnow

b) a 96-hour LC_{50} for shrimp and

c) a 96-hour shell deposition study or a 48-hour EC_{50} test for oyster larvae.

2. Required when there is expected to be direct exposure of aquatic wildlife as a result of direct application to the estuarine or marine environment, or the product is expected to enter this environment in significant concentrations because of its use or mobility pattern.

There are no studies submitted under this Guideline. This requirement is reserved pending receipt of environmental fate data. Products registered for indoor, greenhouse and domestic outdoor uses are exempt from this requirement.

Ecological Effects

The following documents were sent to EEB and received abbreviated reviews. They do not appear in the Topical Summary.

Author(s)	Date	MRID Number
Sanders, H.O.	1972	085219

II. ECOLOGICAL EFFECTS DISCIPLINARY REVIEW

A. Ecological Effects Profile

1. Technical Grade Active Ingredients

a. Toxicity to Birds

Avian acute single dose studies in mallard ducks (Hudson 1984, MRID No. HOOSTA01) with allethrin show the LD_{50} as > 2000 mg/kg. As a result, allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin can be considered as practically nontoxic to birds.

The results of studies by Fink, Beavers, and Grimes (1978, MRID Nos. 123339, 027548, and 027547) indicate that the 8-day dietary LC_{50} in bobwhite quail is 2030 ppm for bioallethrin and > 5620 ppm for D-cis/trans-allethrin. The LD_{50} for mallard ducks tested with D-cis/trans-allethrin is > 5620 ppm.

As a result of the above testing, allethrin, bioallethrin, s-bioallethrin and D-cis/trans-allethrin can be considered as slightly to practically nontoxic to birds.

b. Toxicity to Freshwater Fish

Two citations (Johnson and Finley 1980, MRID No. 003503 and Mauck, Olson, and Marking 1976, MRID No. 122546) report 96-hour LC_{50} values for allethrin, s-bioallethrin, and bioallethrin on 27 warm and coldwater fish species. The LC_{50} values range from 2.6 to 80 ppb. These data indicate that the chemicals are very highly toxic to freshwater fish.

c. Toxicity to Aquatic Invertebrates

Four tests on different aquatic invertebrates reported by Johnson and Finley (1980, MRID No. 003503) show 48-hour and 96-hour LC_{50} values for allethrin ranging from 5.6 ppb for the stonefly to 56 ppb for blackfly larvae. These data indicate that the chemicals are very highly toxic to freshwater invertebrates.

d. Toxicity to Estuarine and Marine Organisms

There were no studies of toxicity to estuarine and marine organisms submitted. There is no requirement for this testing on indoor, and domestic outdoor use products when they are used as directed. The toxicity from other registered uses cannot be assessed at this time.

2. Formulated Products

No nontarget effects studies with formulated products were submitted. While there were no requirements for nontarget testing of formulated products for low tier hazard assessment to nontarget species, simulated or actual aquatic field testing is warranted with the multiple active ingredient formulated products for non-indoor and nondomestic outdoor uses because of the very high toxicity to aquatic organisms shown by the acute toxicity test results. This requirement is reserved pending receipt of environmental fate data.

B. Chemical Properties

1. Technical Grade Products

Allethrin, bioallethrin, S-bioallethrin, and D-cis/trans-allethrin are all common names for a series of active ingredients containing two or more of the eight stereoisomers which comprise 2-allyl-4-hydroxy-3-methyl-3-cyclopenten-1-one ester of 2,2-dimethyl-3-(2-methyl propenyl) cyclopropane carboxylic acid.

Introduced in 1949, allethrin has the distinction of being the first synthetic pyrethroid. Allethrin is merely a synthetic duplicate of Cinerin I (a component of pyrethrum) with a slightly more stable side chain, making it more persistent than pyrethrum. Because of this, allethrin is often referred to as the allyl homologue of Cinerin I. Technical allethrin contains 18 percent of the most active stereoisomer, the D-trans of D-isomer, and 72 percent of the other seven isomers (see Table below). Bioallethrin was introduced in 1969 along with several other second-generation pyrethroids. Since technical bioallethrin contains 46 percent of the most active isomer, it is considerably more efficacious than allethrin. S-bioallethrin, the most potent member of the series, was synthesized in 1972 and contains over 90 percent of the most active isomer.

Composition in Stereoisomers of Some Commercial Compounds in the Allethrin Series (from the Qualitative Use Assessment, Benefits and Use Division)

Common Name	Synonyms	Purity of Technical Material (%)	Actual Content in Allethrin Stereoisomers (%)				
			(DT of D*)	(DT of L)	(DL of D)	(DL of L)	4 Other Isomers
Allethrin	pynamin	90	18	18	4.5	4.5	45
Bioallethrin	d-trans allethrin	93	≥ 46	≥ 46	0.5	0.5	Trace
S-Bioallethrin	esbiol	95	≥ 90	5	--	--	--
D-cis/trans allethrin	pynamin forte	92	36.5	36.5	(----18.4----)		--

*The most biologically active isomer.

Because the four registered chemicals - allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin - all have the most active stereoisomer (D-trans of D-isomer) as the major component, nontarget effects data on any one of the above were used to assess risk on all four compounds.

2. The Formulated Products

The allethrins series (allethrins) are broad spectrum insecticides and acaricides commonly used to control a variety of urban insect pests including cockroaches, ants, flies, mosquitoes, lice, fleas, and ticks. The McLaughlin Gormley King Company and Roussel Uclaf are the primary producers of these materials.

The allethrins are almost always formulated with a synergist and one or more additional active ingredients. Piperonyl butoxide, MGK 264, or 2-hydroxy-ethyl-n-octyl sulfide are typical synergists. The list of active ingredients in allethrins formulations is quite exhaustive, but resmethrin, D-phenothrin, diazinon, malathion, rotenone, and dichlorvos are typical. Refer to Appendix A-1 in the "EPA Index to Pesticide Chemicals" for a complete list of active ingredients found in combination with allethrins.

Allethrins are primarily formulated as pressured liquids, but are also available as mosquito coils, dusts, emulsifiable concentrates, soluble concentrate liquids, and ready-to-use liquids.

The following is a summary of the registered products:

	Allethrin			Bioallethrin			S-Bio-allethrin		D-cis/trans allethrin	
	SAI	MAI	SLN	SAI	MAI	SLN	SAI	MAI	SAI	MAI
Technical	7	-	-	3		-	2	-	3	-
Formulation intermediate	9	65	-	4	45	-	1	25	1	8
Dust	-	1	-	-	3	-	-	-	-	-
Impregnated materials*	3	29	-	3	5	-	-	-	13	2
Emulsifiable concentrate	1	20	1	-	7	-	-	3	-	1
Soluble concentrate/ liquid	-	18	-	-	3	-	-	2	-	1
Ready-to-use liquid	-	49	-	1	94	-	-	22	-	-
Pressurized liquid	-	57	-	-	320	1	-	27	-	20
Total	20	239	1	11	477	1	3	79	17	32

*Includes mosquito coils.
Source: "EPA Index to Pesticide Chemicals"

3. Use Information

Usage data from the Economic Analysis Branch (EAB) of the Benefits and Use Division indicate that domestic dwellings (indoor) and domestic dwellings (outdoor) are high volume sites and commercial establishments are low volume sites. EAB also indicated that small amounts are also applied as pet shampoos and dips. Bioallethrin comprises the largest segment of this market with nearly one-half of the total allethrins usage. Bioallethrin is marketed primarily in the form of indoor room foggers, and plant, carpet, and general purpose aerosols. Allethrin accounts for about a quarter of the usage, mostly in the form of mosquito coils. D-cis/trans-allethrin accounts for another quarter of the usage, mostly in the form of outdoor area foggers. S-bioallethrin comprises less than 3 percent of this market.

Allethrins are also registered for use on a wide variety of agricultural crops, ornamentals, greenhouse crops, stored commodities, domestic and commercial sites, and agricultural premises and equipement. Refer to the "EPA Index to Pesticide Chemicals" for detailed information on registered uses.

a. Indoor Uses

The term Domestic Dwellings (Indoor) refers to indoor areas of single family homes, mobile homes, townhouses, condominiums, apartments, and, to a limited extent, motels, hotels, and tourist courts. There are 80.4 million households in the United States (excluding hotels, motels, and tourist courts).

Allethrin and bioallethrin are registered to control the following pests in domestic dwellings: ants, bedbugs, booklouse, boxelder bug, carpet beetle, centipedes, clover mite, cockroaches, crickets, earwigs, firebrat, fleas, hornets, lice, millipedes, mosquitoes, moths, scorpions, silverfish, sowbugs, spiders, stored product insects, ticks, wasps, and yellowjackets.

Formulations	Dosage Rate
Total release aerosols (0.3-1.2%) (primarily bioallethrin)	0.85-1.06 g active ingredient/ 10,000 cubic feet

Formulations	Dosage Rate
Pressurized spray cans (0.03-0.6%) (primarily bioallethrin)	12 oz of 0.03-0.6% spray per household (1200 sq ft) (equivalent to 0.1 to 2 g/ai/1200 sq ft)
Dusts (0.15-1.8%)	14 to 16 oz of 0.2-0.23 dust per household (1200 sq ft) (0.9 g/ai/1200 sq ft)

	Application Time	Number Applications Year	Hours Per Year
Homeowner:			
Apartment (1000 sq ft)	5 minutes	10	0.83
Single family dwelling (1200 sq ft)	5 minutes	4	0.33

b. Dosmetic Outdoor Uses

The term Domestic Dwellings (Outdoor) refers to external pesticidal treatments to the structure and yard surrounding single family homes, mobile homes, townhouses, and motels and to a limited extent condominiums, apartments, and hotels. Domestic Dwellings (Outdoor) treatments include applications to all exterior portions of the house including foundations, door and window frames, screens, eaves, porches, patios, garage areas, outdoor sheds, etc. It also includes treatment of the yards surrounding the dwelling for household pests. It specifically excludes all treatments to structures against structural pests such as termites and to the yards for pests whose only damage is to the vegetation (e.g., sod webworm, gypsy moth).

The allethrins are registered to control over 30 different invertebrate pests in outdoor situations. Usage data indicate that the D-cis/trans-allethrin outdoor foggers (e.g., Raid Yard Guard) and the allethrin mosquito coils represent the majority of usage for this site. These products are primarily used against flying nuisance pests such as mosquitoes, flies, gnats, and midges.

Formulation		Dosage Rate
Aerosol Outdoor Foggers (0.13-0.24%) (primarily D-cis/trans-allethrin)	16 oz	0.13-0.24% spray

Formulation		Dosage Rate
Mosquito Coils (0.35-0.45%) (primarily allethrin)	4.5 to 5.5 oz package 10 to 12 coils	1 coil/7 hours

Aerosol outdoor foggers and mosquito coils are generally applied once per day. Assuming applications on weekends only, it is conceivable that a homeowner may apply these materials up to 26 times per year.

Duration of Each Application

Aerosol Outdoor Foggers: 15 to 60 seconds (EPA estimate).

Mosquito coils: 7 hours.

c. Risk Assessment: Domestic Indoor/Outdoor Uses

Domestic indoor and domestic outdoor products are not expected to enter the habitat of susceptible aquatic and terrestrial organisms in significant concentrations. Their uses are not expected to pose a risk to nontarget wildlife.

d. Risk Assessment: Other Than Indoor/Domestic Outdoor Uses

In addition to indoor/domestic outdoor uses the four compounds are also registered for terrestrial, aquatic and greenhouse food and nonfood uses, as well as for forestry, under a large number of multiple ingredient formulations (see Section II.B.3). Many of these registrations are for areas and crops that result in exposure of aquatic organisms to which these pesticides are very highly toxic. Aquatic organisms are, therefore, expected to be at risk from many terrestrial/aquatic, food/nonfood and forestry uses. Data for a definitive risk assessment for these registered uses are not available at this time. As a result, the risk of allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin to freshwater fish, freshwater aquatic invertebrates or estuarine and marine organisms, for non-indoor/domestic outdoor uses cannot be assessed. This assessment is reserved pending the receipt of environmental fate data.

EEB may need information from the following tests: freshwater fish LC_{50} (formulated products), acute LC_{50} estuarine and marine organisms, fish early life stage testing, fish life cycle studies, freshwater invertebrate acute LC_{50} (formulated products), and aquatic invertebrate life cycle testing.

Furthermore, it is possible that aquatic field studies will be needed to address multiple active ingredient formulations to determine synergistic or additive effects.

In order to definitively determine the need for the above test data and to perform a final risk assessment EEC's would be necessary. EEB does not have appropriate environmental fate data to perform an EEC. If the properties of the chemicals are such that they persist or move into the aquatic environment, then additive EEB studies will be required for nondomestic use patterns.

C. Precautionary Labeling

1. Manufacturing-Use Product

"This pesticide is highly toxic to fish. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public waters unless this product is specifically identified and addresssed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your local State Water Board or Regional Office of the EPA."

2. End-Use Product

a. Domestic outdoor

"This pesticide is highly toxic to fish. Do not apply directly to water or wetlands (swamps, bogs, marshes, and potholes). Drift from treated areas may be hazardous to organisms in adjacent aquatic sites. Do not contaminate water by cleaning of equipment or disposal of wastes."

b. Indoor

"Do not contaminate water by disposal of wastes."

3. Endangered Species Labeling

There is no endangered species labeling required at this time. Indoor and domestic outdoor use patterns are not expected to impact the habitat of susceptible aquatic organisms in significant concentrations.

Due to a lack of pertinent environmental fate and use information, the risk of allethrin, bioallethrin, s-bioallethrin, and D-cis/trans-allethrin to endangered species from registered terrestrial/aquatic food and nonfood uses, including forestry, cannot be assessed at this time (see Section II.B.3.d).

E. Major Data Gaps

Please see Generic Data Requirement Table.

GENERIC DATA REQUIREMENTS FOR ALLETHRIN, BIOALLETHRIN, S-BIOALLETHRIN, AND D-CIS/TRANS-ALLETHRIN

Data Requirement	Composition[a/]	Use Pattern[b/]	Does EPA Have Data To Satisfy This Requirement (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Period
§158.145 Wildlife and Aquatic Organisms						
Avian and Mammalian Testing						
71-1 - Avian Oral LD_{50}	TGAI	A,B,C,D,E, F,G,H,I	Yes	HCOSTA01	No	
71-2 - Avian Dietary LC_{50}	TGAI	A,B,C,D,E,[1/] F,G,H,I	Yes	123339 027547	No	
71-3 - Wild Mammal Testing	TGAI	A,B,G	No		No	
71-4 - Avian Reproduction	TGAI	A,B,C,D,G,	No		Reserved[2/]	
71-5 - Simulated or Actual Field Testing - Mammals and Birds	TEP	A,B,C,D,G,	No		Reserved[3/]	
Aquatic Organism Testing						
72-1 - Freshwater Fish LC_{50}	TGAI	A,B,C,D,E,[1/] F,G,H,I	Yes	003503	No	
	TEP	C,D	No		Reserved[2/4/]	

GENERIC DATA REQUIREMENTS FOR ALLETHRIN, BIOALLETHRIN, S-BIOALLETHRIN, and D-CIS/TRANS-ALLETHRIN (cont'd)

Data Requirement	Composition[a/]	Use Pattern[b/]	Does EPA Have Data To Satisfy This Requirement (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Period
§158.145 Wildlife and Aquatic Organisms (cont'd)						
72-2 - Freshwater Aquatic						
- Invertebrate LC_{50}	TGAI	A,B,C,D,E, F,G,H,I	Yes	003503	No	
	TEP	C,D	No		Reserved[2/4/]	
72-3 - Acute Estuarine and Marine LC_{50}						
- Fish	TGAI	A,B,C,D,G	No		Reserved[2/5/]	
	TEP	C,D	No		Reserved[2/4/5/]	
- Shrimp	TGAI	A,B,C,D,G	No		Reserved[2/5/]	
	TEP	C,D	No		Reserved[2/4/5/]	
- Oyster	TGAI	A,B,C,D,G	No		Reserved[2/5/]	
	TEP	C,D	No		Reserved[2/4/5/]	

GENERIC DATA REQUIREMENTS FOR ALLETHRIN, BIOALLETHRIN, S-BIOALLETHRIN, and D-CIS/TRANS-ALLETHRIN (cont'd)

Data Requirement	Composition[a/]	Use Pattern[b/]	Does EPA Have Data To Satisfy This Requirement (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Time Period
§158.145 Wildlife and Aquatic Organisms (cont'd)						
72-4 - Fish Early Life Stage and Invertebrate Life Cycle						
- Freshwater	TGAI	A,B,C,D,E, F,G,H,I	No		Reserved[2/6/]	
	TEP	A,B,C,D,G	No		Reserved[2/4/]	
- Estuarine	TGAI	A,B,C,D,G	No		Reserved[2/5/]	
	TEP	C,D	No		Reserved[2/4/]	
72-5 - Fish Life Cycle	TGAI	A,B,C,D,G	No		Reserved[2/]	
	TEP	A,B,C,D,G	No		Reserved[2/4/]	
72-6 - Aquatic Organims Accumulation	TEP	A,B,C,D,G	No		No	
72-7 - Simulated or Actual Field Testing						
- Aquatic Organisms	TEP	A,B,C,D,G,	No		Reserved[2/]	

a/ Composition: TGAI = Technical grade of the active ingredient; PAI = Pure active ingredient; TEP = Typical end product.

b/ The use pattern are coded as follows: A = Terrestrial Food Crop; B = Terrestrial Nonfood; C = Aquatic Food Crop; D = Aquatic Nonfood; E = Greenhouse Food Crop; F = Greenhouse Nonfood; G = Forestry; H = Domestic Outdoor; I = Indoor.

1/ Only one species is required

2/ Reserved pending receipt of the following data: application frequency and timing, environmental stability and movement of compound.

3/ Reserved pending results of avian reproduction study.

4/ Required for aquatic applications and for multiple a.i. formulations for aquatic use.

5/ Required when product is expected to enter estuarine environment in significant concentrations because of use pattern.

6/ Required when aquatic environment is exposed and the fish and aquatic invertebrate LC_{50} is less than 1 mg/L.

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

MAY 13 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Registration Standard for Bioallethrin - Nontarget Insect Studies

FROM: Allen W. Vaughan, Entomologist
Ecological Effects Branch
Hazard Evaluation Division (TS-769-C)

THRU: Henry T. Craven, R.S. Coordinator
Ecological Effects Branch
Hazard Evaluation Division (TS-769-C)

THRU: Michael W. Slimak, Chief
Ecological Effects Branch
Hazard Evaluation Division (TS-769-C)

TO: Richard King, PMT-17
Insecticide/Rodenticide Branch
Registration Division (TS-767-C)

The Ecological Effects Branch has reviewed the nontarget insect data received under the Registration Standard for bioallethrin. Attached material includes DER's, Topical Summary, Disciplinary Review, and Data Table.

It should be noted that, for the purposes of bee toxicity testing, data from any of the following four compounds are considered interchangeable: allethrin, bioallethrin, S-bioallethrin, and D-cis/trans allethrin. Thus, only one disciplinary review and one data table have been developed.

It should also be noted that, despite the fact that allethrin tested moderately toxic to honey bees in one acute study, the requirement for residual toxicity testing will not be imposed. This is because outdoor use rates are so low that even direct application to bees is not likely to result in significant mortality.

Attachments

cc: J. Heckman (MSS/HED)
A. Rispin (SIS/HED)

Bioallethrin Registration Standard - Nontarget Insects

Effects on Beneficial Insects

The following studies received full review under this topic:

Author	MRID #
Atkins and Anderson	00060633
Stevenson	05004151

Studies are outlined in Table 1.

TABLE 1. Toxicity studies on beneficial insects with bioallethrin

Species	Formulation	Results	Author	Date	MRID #
Honey bee (Apis mellifera)	Technical allethrin	Contact LD50= 3.4 micrograms per bee (moderately toxic)	Stevenson	1968	0500415i
Honey bee	Not reported	Not toxic at 10 ug/bee (acute contact)	Atkins and Anderson	1967	00060633

Information from the above studies indicates that allethrin is relatively nontoxic to moderately toxic to honey bees, when bees are exposed to direct treatment. This variability may be attributed to the differences between the two test methods. These studies fulfill the guideline requirement for a honey bee acute contact study.

The following studies received abbreviated reviews:

Author	MRID#
Univ. of Calif.	00049252
Atkins and Anderson	00049254
Anderson et al.	05003871

Statements for Disciplinary Review

Effects on Beneficial Insects

In laboratory acute contact studies, allethrin was shown to be relatively nontoxic (Atkins and Anderson 1967) and moderately toxic (Stevenson 1968). This difference can probably be attributed to differences in test methodology.

References (for Disciplinary Review)

Atkins, E.L., Jr.; Anderson, L.D. (1967) Toxicity of Pesticides and Other Agricultural Chemicals to Honey Bees: Laboratory Studies. ?: Univ. of California, Agricultural Extension Service. (M-16; submitter report No. 22259; also in unpublished submission received Mar 27, 1974 under 4F1485; submitted by Chemagro Corp., Kansas City, MO.; CDL: 092011-N). MRID# 00060633

Stevenson, J.H. (1968) Laboratory studies on the acute contact and oral toxicities of insecticides to honeybees. Annals of Applied Biology 61(3): 467-472. MRID# 05004151

TABLE A
GENERIC DATA REQUIREMENTS FOR BIOALLETHRIN

ca Requirements	Composition[1/]	Use Pattern[2/]	Does EPA Have Data to Satisfy This Requirement? (Yes, No or Partially)	Biblio-graphic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? [3/]
§158.155 Nontarget Insect					
NONTARGET INSECT TESTING - POLLINATORS:					
141-1 - Honey bee acute contact LD50	TGAI	A,B,H	Yes	00060633 05004151	No
141-2 - Honey bee - toxicity of residues on foliage	TEP	A,B,H	No		No[4/]
141-4 - Honey bee subacute feeding study	[Reserved][5/]				
141-5 - Field testing for pollinators	TEP	A,B,H	No		No
NONTARGET INSECT TESTING - AQUATIC INSECTS:					
142-1 - Acute toxicity to aquatic insects	[Reserved][6/]				
-2 - Aquatic insect life-cycle study	[Reserved][6/]				
142-3 - Simulated or actual field testing for aquatic insects	[Reserved][6/]				
143-1 thru 143-3 - NONTARGET INSECT TESTING - PREDATORS AND PARASITES	[Reserved][6/]				

1/ Composition: TGAI = Technical grade of the active ingredient; TEP = Typical end-use product.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor.
3/ Data must be submitted no later than _____.
4/ Although allethrin showed moderate bee toxicity in one acute test, outdoor use levels are so low that bee toxicity is not a concern. Thus, residual toxicity data will not be required.
5/ Reserved pending development of test methodology.
6/ Reserved pending Agency decision as to whether the data requirement should be established.

ANNUAL ALLETHRIN

CASE: GS0410 BIOALLETHRIN

CONT-CAT: 01 GUIDELINES: 142-3

MRID: 60633

Atkins, E.L., Jr.; Anderson, L.D. (1967) Toxicity of Pesticides and Other Agricultural Chemicals to Honey Bees: Laboratory Studies. ?: Univ. of California, Agricultural Extension Service. (M-16; submitter report no. 22259; also°In°unpublished submission received Mar 27, 1974 under 4F1485; submitted by Chemagro Corp., Kansas City, Mo.; CDL:092011-M)

REVIEW RESULTS:

VALID__X__ INVALID_____ INCOMPLETE_____

GUIDELINE: SATISFIED _X_ PARTIALLY SATISFIED _____ NOT SATISFIED___

DIRECT RVW TIME = START DATE: 5/7/87 END DATE: 5/7/87

REVIEWED BY: Allen W. Vaughan

TITLE: Entomologist

ORG: EEB/HED

LOC/TEL: Crystal Mall #2 / 557-0783

SIGNATURE: Allen W. Vaughan DATE: 5/7/87

APPROVED BY:

TITLE:

ORG:

LOC/TEL:

SIGNATURE: DATE:

1. CHEMICAL: Multiple chemicals. See tables.

2. FORMULATION: Variable, mixed with pyrolite dust.

3. CITATION:

Atkins, E.L., Jr., and L.D. Anderson. 1967. Toxicity of pesticides and other agricultural chemicals to honey bees: laboratory studies. (Unpublished study received Jan. 30, 1969 under 9G0802; prepared by Univ. of California-Riverside, Dept. of Entomology, submitted by Hercules, Inc., Agricultural Chemicals, Wilmington, Del.; CDI: 093111 - D) ID 00001999

4. REVIEWER: Allen W. Vaughan
Entomologist
EEB/HED

5. DATE REVIEWED: December 3, 1979

6. TEST TYPE: Honey bee acute contact LD_{50}

A. Test Species: Honey bee (Apis mellifera)

7. REPORTED RESULTS:

Results are reported in the tables. Pesticides are grouped according to their relative toxicity to honey bees, i.e., highly toxic, moderately toxic, or relatively non-toxic. Allethrin (#150) was not toxic to bees at 10 micrograms per bee.

8. REVIEWER'S CONCLUSIONS:

This study is scientifically sound, and shows allethrin to be relatively nontoxic to honey bees . This study fulfills the guideline requirement for an acute contact toxicity test on honey bees.

Materials and Methods

Test Procedures

A bell-jar vacuum duster, is used to apply the pesticide, mixed with a pyrolite dust diluent, to the test bees. Dosages of dust are weighed, bees are aspirated into dusting cages and treated, and bees are then transferred into holding cages. Observations are recorded at 12, 24, 48, 72, and 96 hours.

Statistical Analysis

Analysis of the data was performed to enable the authors to determine LD_{50} values of pesticides from either dosage-mortality curves or from LC_{50} values. The slope value was also obtained from the dosage-mortality curve.

Discussion/Results

See tables for LD_{50} values, slope values, and toxicity categories.

Reviewer's Evaluation

A. Test Procedure

Procedures were scientifically sound.

B. Statistical Analysis

Analysis as performed by the authors was assumed to be valid. No validation was performed by EEB.

C. Discussion/Results

This study is scientifically sound. See tables for results.

TABLE 1

LD_{50} and slope values[8] showing the comparative toxicity of pesticides to honey bees in the laboratory at 48 hours at 80 F (26.7 C) and 65 percent relative humidity.

Pesticide	LD_{50} in ug/bee	Slope Value
Group I - Highly Toxic To Honey Bees		
1 tepp	0.001	0.64
2 Zinophos [5]	0.042	9.08
3 Dursban [5]	0.114	7.80
4 dieldrin[1]	0.139	4.65
5 Furadan , NIA 10242[6]	0.160	4.31
6 parathion[1]	0.175	7.66
7 GC-650	0.178	8.19
8 dimethoate[1], Cygon	0.188	5.94
9 GS-13005[6]	0.236	9.06
10 Temik [5]	0.285	5.64
11 Sumithion [5]	0.288	5.58
12 Bidrin [5]	0.300	16.50
13 Bayer 77488[6]	0.305	6.80
14 fenthion[1], Baytex [5]	0.308	7.20
15 Zectran [5]	0.308	4.92
16 Azodrin [5]	0.350	7.77
17 fensulfothion[5], Dasanit	0.350	5.46
18 aldrin[1]	0.353	4.98
19 mevinphos[1], Phosdrin [5]	0.360	7.96
20 diazinon[1]	0.372	8.97
Mesurol [5]	0.375	3.20
IA-10586[6]	0.408	4.26
famphur[1], Famophos [5]	0.417	4.85
24 Mabam	0.423	8.69
25 azinphosmethyl[1], Guthion [5]	0.423	6.84
26 methyl parathion[1]	0.465	7.28
27 Isolan [5]	0.471	8.70
28 CP-47114[6]	0.477	4.30
29 naled[1], Dibrom [5]	0.480	18.18
30 dichlorvos[1], Vapona [5],DDVP[6]	0.495	8.97
31 heptachlor[1]	0.526	5.16
32 GS-12968[6]	0.550	8.91
33 lindane[1]	0.562	5.07
34 NIA-11637[6]	0.609	3.53
35 NIA-10559[6]	0.624	4.50
36 UC-8305[6]	0.628	2.68
37 malathion[1]	0.709	8.04
38 Bomyl [5]	0.743	9.09
39 Hercules 13462[6]	0.829	3.90
40 UC-10854[6], Hercules 5727[6]	0.937	4.34
41 Methyl Iso-Systox[6]	0.937	3.48
42 azinphosethyl[1], Ethyl Guthion [5]	0.981	7.32
43 Imidan [5]	1.064	4.77
44 RP-11783[6]	1.076	7.11
45 Matacil [5]	1.160	3.72
46 carbaryl[1], Sevin [5]	1.336	2.45
47 Baygon [5]	1.354	3.30
48 Gardona	1.354	30.00
49 RE-9006[6]	1.365	10.32
50 AC-12008[6]	1.380	3.60
51 phosphamidon[1], Dimecron [5]	1.462	14.28
52 Methyl Trithion [5]	1.462	6.64
53 Iso-Systox[6]	1.487	1.45
54 Abate [5]	1.547	2.85
55 Isodrin[1]	1.607	2.63
56 Hercules 9007[6]	1.656	3.30
57 Dow ET-15	1.825	6.12
Group II - Moderately Toxic to Honey Bees		
58 endrin[1]	2.018	4.20
59 RE-5030[6]	2.079	5.28
60 Hercules 3895G[6]	2.248	2.84
61 Ciodrin [5]	2.260	17.10
62 AC-12009[6]	2.284	3.48
63 Agritox [5], trichloronate[5]	2.333	3.26
64 Banol [6]	2.357	5.91
65 N-4543[6]	2.478	2.76
66 demeton[1], Systax [5]	2.598	1.85
67 EI-43064[6]	2.623	4.55
68 G-30494	2.695	4.06
69 Pyramat [5]	2.949	4.07
70 oxydemetonmethyl[1], Meta-Systox-R [5]	2.997	2.32
71 EI-47470[6]	3.505	6.28
72 TD-72[6]	3.578	4.32
73 Bayer 38156[6], ENT-25713[6]	3.602	2.10
74 Bayer 39011[6], ENT-25635[6]	3.747	3.68
75 GS-10128[6]	3.837	6.21
76 Thiodan 1[6]	3.868	2.28
77 UC-6812	3.940	3.75
78 GC-9160[6]	4.085	3.98
79 GC-10284[6]	4.194	3.21

NOTATIONS FOR TABLES ARE AS FOLLOWS

[1] ...n name
[2] ...mark name or other names
[3] Company code designation
[7] Nontoxic at field dosages (below 10 micrograms per bee)
[8] Dosages more critical with material with a high slope value.

Pesticide	LD_{50} in ug/bee	Slope Value
oup II - continued		
80 EI-47031	4.230	7.32
81 TD-73[6]	4.291	5.64
82 carbophenothion[1], Trithion [5]	4.472	8.39
83 Perthane [5]	4.472	4.05
84 endosulfan[1], Thiodan [5]	4.496	3.60
85 GC-9879[5]	4.895	4.14
86 SD-7438[6]	5.076	6.09
87 disulfoton[1], Di-Syston [5]	5.137	1.14
88 chlordane[1]	5.233	3.24
89 UC-340963[6], UC-27074S[6]	5.354	2.75
90 SD-8448[6]	5.739	8.72
91 ronnel[1], Korlan [5], Trolene	5.739	2.10
92 GC-10101[6]	5.776	8.58
93 Thiodan II[6]	5.838	2.91
94 dimetilan[1], Dimetilan [5]	5.838	4.08
95 DDT[1]	5.946	4.89
96 fenoflurazole[6]	6.526	3.40
97 NPD[6]	6.768	3.38
98 mirex[1]	7.145	3.23
99 GC-3583[6], SD-8210[6]	7.735	3.57
00 endothion[1]	8.001	7.02
- Tranid [5]	8.096	3.27
hosalone [5]	8.939	3.83
- HRS-1422[6]	9.548	3.20
4 phorate[1], Thimet [5]	10.07	1.34
5 Kepone [5]	10.39	4.83
oup III - Relatively Nontoxic to Honey Bees		
6 CP-10502[6]	11.00	3.62
7 menazon[1], Saphos [5]	11.06	2.03
8 binapacryl[1], Morocide [5]	11.60	9.97
9 sabadilla[5]	12.33	6.20
0 CP-10515[6]	14.50	3.20
1 ethion[1], Nialate [5]	20.55	0.95

Pesticide	LD_{50} in ug/bee	Slope Value
Group III - continued		
112 dioxathion[1], Delnav [5]	21.27	5.05
113 methoxychlor[1]	23.57	1.55
114 Bayer 39731[6]	26.59	1.27
115 Hercules 14503[6]	34.45	1.30
116 Dilan [5]	40.49	1.70
117 Dowco 213[6]	40.49	3.88
118 ziram[1], Zerlate [5]	46.65	2.12
119 Dessin [5], dinobuton[5]	48.42	5.90
120 toxaphene[1]	50.40	1.67
121 trichlorfon[1], Dipterex [5], Dylox [5]	59.83	2.81
122 GC-3582[6]	60.43	4.92
123 GC-10435[6]	62.80	9.45
124 Morestan [5]	66.47	1.36
125 SG.68[6]	67.08	2.18
126 thiram[1], Arasan [5]	73.72	1.18
127 calcium arsenate	78.56	4.10
128 Dri-die [5]	96.69	4.40
129 GC-8993[6]	96.69	1.37
130 GC-9832[6]	98.00	2.68
131 SG-78[6]	108	3.18
132 CMU	110	0.78
133 Eradex [5]	121	1.14
134 dicofol[1], Kelthane [5]	145	1.52
135 TDE[1], Rothane [5], DDD[6]	161	0.98
136 SG-77[6]	163	2.65
137 Q-128[6]	179	0.75
138 Polyram [5]	437	1.53
139 fenson[1], Murvesco [5]	483	0.065
140 SG-74[6]	880	0.99
141 sulfur	1,051	1.38
142 chlorobenzilate[1]	1,849	1.01
143 dinitrocyclohexylphenol[1], Dinex [5]	2,175	0.45
144 SG-63[6]	3,625	0.91
145 GC-6936[6]	10,031	0.63

Table 2

Pesticides which are not toxic at 10 micrograms per honey bee in the laboratory at 48 hours at 80 F (26.7 C) and 65 percent relative humidity. Group III - Relatively Nontoxic to Honey Bees.

146 Acti-Dione Oxime
147 AL-11
148 AL-15
149 AL-21
150 allethrin [1,7]
151 ALQ-221
152 amitrol, AT
153 ARL-15
154 Bacillus thuringiensis Berliner
155 Bayer 28589
156 Bayer 47531
157 C-940
158 captan
159 CDAA, Randox ®
160 CDEC, Vegedex [1] ®
161 chlorbenside [1], Chloroparacide ® [5], Mitox ® [5]
162 coppper oxychloride sulfate
163 cryolite
164 cuprous oxide
165 cyprex
166 2,4-D
167 D-6
168 dalapon
169 DDT antiresistent
170 2,4-DEB, Sesin ®
171 DEF ® [5]
172 Dexonn ® [5]
173 dicamba [1], Banvel D ®
174 diuron, Karmex ®
175 DL-15
176 DMTT, Mylone ®
177 Dyrene ® [5], Kemate ® [6]
178 EPTC, Eptam ®
179 ferbam
180 folcid, Difolitan ®
181 Falex ®, merphos
182 folpet, Phalton ®
183 GC-2066
184 GC-2131
185 GC-10379
186 glyodin, [6] Glyoxide ®
187 GS-13798 [6]
188 GS-19851 [6], ENT-27552
189 Heliothis virus
190 maneb
191 MCPA
192 metallic thiocyanate
193 methyl chlorobenzilate
194 nabam
195 Nemagon ®, Fumazone ®
196 nicotine
197 NPA
198 olancha clay
199 Omite ®
200 ovex [1], Ovatran ® [5]
201 Paraquat ®
202 phygon, dichlone
203 Planavin ®
204 PREP ® [5]
205 pyrethrin [1,7]
206 rotenone [1,7]
207 sesone
208 silikil
209 simazin
210 2,4,5-T
211 2,3,6-TBA, Trysben ®
212 TD-71
213 tetradifon [1], Tedion ® 5
214 Triton B-1956 ®
215 Triton X-100 ® [6]
216 UC-21426 [6]
217 UC-21427 [6]

004001 ALLETHRIN MULTIPLE

TDMS0030 DATA EVALUATION RECORD PAGE 1 OF 5

CASE GS0014 ~~ENDOSULFAN~~ ALLETHRIN PM 110 08/12/79

CHEM ~~079401~~ 004001 Endosulfan (hexachlorohexahydromethanol)

BRANCH EEB DISC 40 TOPIC 10000045 GUIDELINE CFR

FORMULATION 00 - TECHNICALS

FICHE/MASTER ID 05004151 CONTENT CAT 03

Stevenson, J.H. (1968) Laboratory studies on the acute contact and oral toxicities of insecticides to honeybees. Annals of Applied Biology 61(3):467-472.

SUBST. CLASS = S.

OTHER SUBJECT DESCRIPTORS
SEC: EEB -40-05050045

DIRECT RVW TIME = 4 hr. (MH) START-DATE Feb 15, 1980 END DATE Feb 15, 1980

REVIEWED BY: Allen W. Vaughan
TITLE: Entomologist
ORG: EEB/HED
LOC/TEL: Crystal Mall #2, 557-1405

SIGNATURE: Allen W. Vaughan DATE: 11/4/80

APPROVED BY:
TITLE:
ORG:
LOC/TEL:

SIGNATURE: DATE:

CONCLUSIONS: This study is scientifically sound. See tables for results.

METHODS AND MATERIALS:

A. Test Type - Toxicity to honey bees
B. Test Species - Honey Bee (Apis mellifera)
C. Test Procedures -

1. Contact toxicity tests

Test bees were anesthetized with CO_2 and placed in cylindrical wire mesh cages (10 bees per cage). Bees were maintained in the cages and fed sucrose solution.

For insecticide testing, bees were again anesthetized with CO_2 (in the cages), then laid separately on filter paper. One microliter drops of pesticide/solvent mixture were then applied to the thorax with a microapplicator. Mortality was recorded 24 hours after treatment.

2. Oral toxicity tests

As in the contact tests, groups of 10 bees were placed in wire cages. Insecticides were presented to the groups in acetone/sucrose/water solutions, each group receiving 0.2 ml of the solution.

When bees had taken all the insecticide solution, they were provided with 20% sucrose. Mortality was evaluated 24 hours after initial dosage.

3. Statistical Analysis

(Author's description)

To obtain regression lines, two lots of ten bees treated with each of five or six concentrations of poison were used after preliminary experiments established the range. LD_{50} (median lethal dose) values were calculated using the probit method (Finney, 1952) and Table I gives means for the LD_{50} values and for the slopes of the calculated regression lines. The number of regression assays used to obtain the figures quoted is also given in the table. The standard errors of the estimated average LD_{50}'s depend on the variation between the results of the individual experiments. Because of the small number of degrees of freedom between experiments for each type of insecticide, a pooled within-treatment estimate of the percentage standard deviation (S.D.) was calculated for each year. Thus the percentage standard error for an individual LD_{50} or slope value in the table is given by $(S.D./\sqrt{n})\%$; for the contact LD 50 for mevinphos in 1964, this standard error is $(27/\sqrt{6})\%$, i.e. 11%. Values for LD_{90} (the dose required to kill 90% of the insects) were calculated from the mean slope and LD_{50} values.

REPORTED RESULTS: Laboratory LD_{50}'s derived from contact and oral exposure are presented in tables 1 and 2, respectively. Data were developed from 3 years of testing with 21 pesticide compounds.

See table 1 and 2 for presentation numerical data.

DISCUSSION:

A. Test Procedure
Procedure is sound.

B. Statistical Analysis
Analysis as performed by the author was assumed to be valid. No validation was performed by EEB.

C. Discussion/Results
This study is scientifically sound.

Table 1. Acute contact toxicity of some pesticides to worker honeybees determined in the laboratory during 1964, 1965 and 1966

Mean median lethal doses (LD_{50}) expressed as ug compound per insect and mean slopes of regression lines, n is number of regression lines used to obtain each mean. LD_{90} values derived from these means are also given.

	1964				1965				1966			
	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope
Azinphos-methyl	—	—	—	—	—	—	—	—	2	0.063	0.13	4.0
Mevinphos	6	0.070	0.10	7.3	—	—	—	—	—	—	—	—
'Bidrin'	1	0.076	0.10	9.6	—	—	—	—	—	—	—	—
Dimethoate	3	0.12	0.17	8.4	9	0.11	0.14	11	7	0.098	0.15	7.4
Dieldrin	8	0.16	0.23	7.6	6	0.16	0.26	6.0	—	—	—	—
Diazinon	2	0.22	0.30	9.4	—	—	—	—	—	—	—	—
Malathion	2	0.27	0.38	8.5	3	0.22	0.32	8.1	—	—	—	—
Pyrethrins	4	0.29	0.45	6.6	4	0.13	0.20	4.4	—	—	—	—
Phorate	3	0.32	0.42	11	—	—	—	—	2	0.33	0.57	5.3
BHC	3	0.46	0.68	7.4	6	0.20	0.33	5.8	—	—	—	—
Demeton-methyl	3	0.74	0.90	15	1	0.41	0.52	12	3	0.54	0.95	5.2
Endrin	—	—	—	—	3	1.2	2.1	4.9	2	0.65	1.5	3.6
Carbaryl	2	1.3	7.4	1.7	1	1.1	1.5	0.96	—	—	—	—
Chlordane	3	1.4	1.9	10	—	—	—	—	—	—	—	—
Carbophenothion	—	—	—	—	—	—	—	—	2	1.4	6.6	1.9
Allethrin	4	3.4	4.6	9.7	—	—	—	—	—	—	—	—
DDT	3	3.9	6.2	6.4	—	—	—	—	—	—	—	—
Disulfoton	3	4.1	5.9	8.1	4	4.3	8.0	4.7	2	5.0	6.8	9.4
Menazon	3	4.3	8.1	3.0	—	—	—	—	—	—	—	—
Endosulfan	4	7.1	13	4.6	—	—	—	—	—	—	—	—
Ethyl mercury chloride	2	22	43	4.4	—	—	—	—	—	—	—	—
Standard deviation (%)		27		23		21		24		20		20

Table 2. Acute oral toxicity of some pesticides to worker honeybees determined in the laboratory during 1964, 1965 and 1966

Mean median lethal doses (LD_{50}) expressed as ug compound per insect and mean slopes of regression lines, n is number of regression lines used to obtain each mean. LD_{90} values derived from these means are also given.

	1964				1965				1966			
	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope	n	Mean LD_{50} (ug)	LD_{90} (ug)	Mean slope
Mevinphos	3	0.027	0.057	3.9	—	—	—	—	—	—	—	—
'Bidrin'	3	0.068	0.20	2.7	—	—	—	—	—	—	—	—
Dimetho	—	—	—	—	8	0.15	0.31	4.0	6	0.13	0.34	3.1
Azinph[illegible]methyl	—	—	—	—	—	—	—	—	3	0.15	0.28	4.7
Cabaryl	2	0.14	0.26	4.8	2	0.11	0.39	2.3	—	—	—	—
Pyrethrins	2	0.15	0.61	2.1	2	0.15	0.41	2.9	—	—	—	—
Diazinon	2	0.20	0.68	2.4	—	—	—	—	—	—	—	—
Dieldrin	6	0.32	0.66	4.1	3	0.33	0.94	2.8	—	—	—	—
Malathion	3	0.38	0.88	3.5	—	—	—	—	—	—	—	—
Phorate	4	0.44	0.90	4.1	—	—	—	—	1	0.43	0.79	4.8
BHC	1	0.45	2.5	1.7	1	0.76	2.7	2.3	—	—	—	—
Menazon	2	0.46	0.77	5.7	—	—	—	—	—	—	—	—
Demeton-methyl	3	0.61	1.0	5.5	2	0.83	1.8	3.9	2	0.58	1.2	4.2
Endrin	—	—	—	—	2	1.4	2.8	4.2	2	0.46	1.0	3.7
DDT	3	3.7	7.5	4.2	—	—	—	—	—	—	—	—
Carbophenothion	—	—	—	—	—	—	—	—	2	5.2	10	4.2
Endosulfan	3	6.9	43	1.6	—	—	—	—	—	—	—	—
Allethrin	2	9.1	20	3.8	3	4.6	10	3.8	—	—	—	—
Phenyl mercury acetate	2	10	32	2.5	—	—	—	—	—	—	—	—
Ethyl mercury chloride	1	13	18	9.2	—	—	—	—	—	—	—	—
Disulfoton	2	16	38	3.4	1	23	41	5.0	1	39	54	9.9
Standard deviation (%)		35		55		22		33		43		41

DATA EVALUATION RECORD PAGE 1 OF 1

CASE: GS0410 BIOALLETHRIN

CONT-CAT: 01 GUIDELINES: 141-1

MRID: 49252

University of California, Agricultural Extension Service (19??) Toxicity of Pesticides and Other Agricultural Chemicals to Honey Bees: Field Study. Riverside. Calif.: UC, ACES. (AXT-251; submitter report no. 21052; also°In°unpublished submission received Mar 22, 1976 under 3125-71; submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL:224114-I)

REVIEW RESULTS:

VALID_____ INVALID_____ INCOMPLETE_____

GUIDELINE: SATISFIED ___ PARTIALLY SATISFIED _____ NOT SATISFIED___

DIRECT RVW TIME = START DATE: 5/7/87 END DATE: 5/7/87

REVIEWED BY: Allen W. Vaughan

TITLE: Entomologist

ORG: EEB/HED

LOC/TEL: Crystal Mall #2 / 557-0783

SIGNATURE: Allen W. Vaughan DATE: 5-7-87

APPROVED BY:

TITLE:

ORG: Duplicate Study

LOC/TEL: Information provided in this study was reviewed under MRID# 00060633.

SIGNATURE: DATE:

DATA EVALUATION RECORD PAGE 1 OF 1

CASE: GS0410 BIOALLETHRIN

CONT-CAT: 01 GUIDELINES: 141-1

MRID: 49254

Atkins, E.L., Jr.; Anderson, L.D. (1967) Toxicity of Pesticides and Other Agricultural Chemicals to Honey Bees: Laboratory Studies. By Univ. of California--Riverside, Dept. of Entomology. Riverside, Calif.: UC, Agricultural Extension Service. (M-16; submitter report no. 22259, also°In°unpublished submission received Mar 22, 1976 under 3125-71; submitted by Mobay Chemical Corp, Kansas City, Mo.; CDL:224114-K)

REVIEW RESULTS:

VALID_____ INVALID_____ INCOMPLETE_____

IDELINE: SATISFIED ___ PARTIALLY SATISFIED ____ NOT SATISFIED___

DIRECT RVW TIME = START DATE: 5/7/87 END DATE: 5/7/87

REVIEWED BY: Allen W. Vaughan

TITLE: Entomologist

ORG: EEB/HED

LOC/TEL: Crystal Mall #2 / 557-0783

SIGNATURE: Allen W. Vaughan DATE: 5-7-87

APPROVED BY:

TITLE:

ORG: Duplicate Study

LOC/TEL: Information provided in this study was reviewed under MRID# 00060633.

SIGNATURE: DATE:

TDMS0030 DATA EVALUATION RECORD PAGE 1 OF

CASE GS0008 ~~DICHLONE & (07/16/79)~~ ALLETHRIN PM 11C 08/27/79

CHEM ~~029601~~ 004001 Dichlone (2,3-dichloro-1,4-naphthoquin

BRANCH EEB DISC 40 TOPIC 05000045

FORMULATION 00 - ACTIVE INGREDIENT

FICHE/MASTER ID 05CC3871 CONTENT CAT 12

Anderson, L.D.; Atkins, E.L., Jr.; Todd, F.E.; McGregor, S.E. (1962) Toxicity of pesticides to honeybees. Gleanings in Bee Culture 90(1):152-153.

SUBST. CLASS = S.

DIRECT RVW TIME = 15 min(MH) START-DATE END DATE

REVIEWED BY: Allen W. Vaughan 10/10/79 10/10/79
TITLE: Entomologist
ORG: EEB/HED
LOC/TEL: Crystal Mall #2/71405

SIGNATURE: Allen W. Vaughan DATE: 10/31/79

APPROVED BY:
TITLE:
ORG:
LOC/TEL:

SIGNATURE: DATE:

STUDY NOT PERTINENT

This study is a review and does not contain original data.

END