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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cover Memo for Bioallethrin Registration Standard

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Four allethrins are addressed in the Bioallethrin Registration Standard. These allethrins consist of mixtures of eight stereoisomers. Two of the isomeric mixtures, Bioallethrin and s-Bioallethrin (Esbiol) contain two major isomers in different proportions. The third isomeric mixture, d-cis/trans Allethrin mainly contains four isomers and the fourth isomeric mixture, Allethrin contains eight isomers. The isomers are the d/l-cis/trans chrysanthemic acids of d/l-allethrolone. The major producers of the allethrins are the McLaughlin Gormley King Company, Sumitomo Chemical Company and Roussel Uclaf.

The allethrins are broad spectrum insecticides and acaricides commonly used to control a variety of urban insect pests including cockroaches, ants, fleas, flies, mosquitoes, lice and ticks. 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

and food handling establishments, and also has domestic indoor and outdoor uses as well as aquatic and forestry uses. At the present time, d-cis/trans allethrin is used on terrestrial and greenhouse nonfood crops as well as 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).

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). D-cis/trans allethrin accounts for another quarter of the usage (outdoor air foggers). The others are considered to be minor uses.

The allethrins are formulated as dusts, impregnated materials (such as mosquito coils), emulsifiable concentrates, soluble concentrate/liquids, ready-to-use liquids and pressurized liquids.

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, and use of allethrins in food handling establishments.

ECOLOGICAL EFFECTS

Terrestrial

The allethrins 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. Allethrin is practically nontoxic to waterfowl in acute studies and practically nontoxic to slightly toxic to birds in subacute studies. No other avian studies are required for the Registration Standard. Domestic indoor and domestic outdoor products are not expected to enter the habitat of susceptible terrestrial organisms in significant

concentrations. 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 technical Allethrin, s-Bioallethrin and Bioallethrin are very highly toxic to both coldwater and warmwater fish species. In addition, the available data indicate that technical Allethrin is very highly toxic to freshwater aquatic invertebrates.

No other studies are required for these organisms. Domestic indoor and outdoor products are not expected to enter the habitat of susceptible aquatic organisms in significant concentrations. Their uses are not expected to pose a risk to nontarget wildlife. Due to the high toxicity, precautionary labeling is required for fish for both the manufacturing-use product and the end-use product. No specific labeling is required for endangered species.

Ecological Effects Data Requirement Summary

No new data are required for domestic indoor and outdoor uses.

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 Bioallethrin, Allethrin, s-Bioallethrin and d-cis/trans Allethrin. No data were reviewed for any of the required studies.

Re-entry

D-cis/trans Allethrin and s-Bioallethrin do not meet the exposure criteria of 40CFR §158.140 in that they are not used on crops where human exposure could occur, and available toxicology data do not indicate that they meet any of the toxicity criteria. No data are required. Bioallethrin and Allethrin do meet the exposure criteria in that they are used on crops where human exposure could occur, but available toxicology data do not indicate that they meet any of the toxicity criteria. 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. No data are required at this time.

Groundwater

No data are currently available to assess the potential for any of the allethrins to contaminate groundwater.

Environmental Fate Data Requirements

The following list summarizes the data requirements for each of the allethrins.

hydrolysis (all allethrins)
water photodegradation (all allethrins)
soil photodegradation (Bioallethrin and Allethrin)
aerobic metabolism in soil (all allethrins)
anaerobic metabolism in soil (Bioallethrin, and Allethrin)
anaerobic metabolism in water (Allethrin)
aerobic metabolism in water (Allethrin)
leaching and adsorption/desorption (all allethrins)
field dissipation (soil) (all allethrins)
field dissipation (aquatic sediment) (Allethrin)
field dissipation (soil, long-term) (may be required for Bioallethrin and Allethrin depending upon the results of field dissipation studies on terrestrial food crops and aerobic soil metabolism studies)
accumulation studies on rotational crops (confined) (Bioallethrin and Allethrin
accumulation studies on rotational crops (field) (may be required for Allethrin and Bioallethrin if significant residues of concern are found in the confined rotational crop study)
accumulation studies on irrigated crops (Bioallethrin for cranberries and Allethrin if treated water is used for irrigation)
accumulation studies in fish (all allethrins)
accumulation studies in aquatic nontarget organisms (Bioallethrin to support the use on cranberries and Allethrin)
other exposure data may be required if toxicology data indicates the need for additional data

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 Allethrin 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.

Residue Chemistry Data Requirement Summary

For each data requirement listed below, the specific allethrin to be tested will be the one in which its particular use (a use relating specifically to the data requirement) will provide the maximum amount of residue in foods. It is assumed that the results of the studies will be similar for any of the other allethrins with similar use patterns. For example, if both Bioallethrin and Allethrin are used in crops but Allethrin is used in greater amounts, then the field crop trials would be conducted on Allethrin.

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

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 allethrins. 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 d-cis/trans Allethrin. 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 d-cis/trans Allethrin 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 allethrins except for the specific studies mentioned above. In addition, 21-day dermal studies are required for all the allethrins 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 d-cis/trans Allethrin. 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, d-cis/trans Allethrin did not prove to be an oncogen.

A six-month dog feeding study was conducted on Bioallethrin. Since this study was conducted prior to the Subpart F Guidelines, it 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 allethrins. 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 allethrins 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 d-cis/trans Allethrin.

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 allethrins 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 allethrins. 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 allethrins.

Special Studies - Metabolism

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

Toxicology Data Requirement Summary

Acute toxicity

Acute oral LD_{50} toxicity (Allethrin, d-cis/trans Allethrin)
Acute dermal LD_{50} toxicity (Allethrin, d-cis/trans Allethrin, s-Bioallethrin, Bioallethrin)
Acute inhalation LC_{50} toxicity (all allethrins)
Eye irritation (all allethrins except Esbiothrin)
Dermal irritation (all allethrins except Esbiothrin)
Dermal sensitization (all allethrins)

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

Subchronic Toxicity

90-day feeding
  Rodent (all allethrins except d-cis/trans Allethrin)
  Nonrodent (all allethrins except Bioallethrin)
21-day dermal (all allethrins)
90-day inhalation (reserved for all allethrins)

Chronic Toxicity

Rodent feeding (all allethrins except d-cis/trans Allethrin)
Nonrodent feeding (all allethrins except Bioallethrin)
Rat oncogenicity (all allethrins except d-cis/trans Allethrin)
Mouse oncogenicity (all allethrins)
Rat teratogenicity (all allethrins except Bioallethrin)
Rabbit teratogenicity (all allethrins)
Reproduction (all allethrins)

Mutagenicity

Gene mutation (Allethrin, d-cis/trans Allethrin, s-Bioallethrin)
Chromosomal aberration (all allethrins)
Other mechanisms of mutagenicity (all allethrins except Bioallethrin)

Special Testing

Metabolism (all allethrins)