BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Indole
PC Code 025000

U.S. Environmental Protection Agency
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division

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I. EXECUTIVE SUMMARY:

Indole, a new active ingredient, is a naturally-occurring, aromatic substance that is responsible for the fecal odors associated with human waste. As all animal waste contains indole, as do some plants and other naturally-occurring substances, it is ubiquitous in the environment. At high concentrations, it gives off the odor of feces but at lower concentrations, it smells flowery. For this reason, it is a common ingredient in perfumes and synthetically-produced essential oils, such as jasmine oil. Indole is also a major constituent of coal tar, the main industrial source, but was first isolated from indigo for use as a dyestuff.

In its pure form, indole is irritating to the eyes and skin and it may be fatal if swallowed or contacted by the skin. According to the Material Data Safety Sheet (MSDS) for indole, the acute oral LD_{50} is 1000mg/kg. The concentrated vapor of indole is irritating to the throat and lungs. The proposed use pattern, as a component of a fly attractant, however, utilizes only minute quantities of indole that are much lower in concentration than many naturally-occurring essential oils or human feces. In the proposed product, Bull Run Fly Attractant, indole is enclosed with other active ingredients in a water-soluble, vapor-barrier pouch that will be placed in a fly trap so there is little to no anticipated exposure. At the proposed concentration of 0.2%, even at the maximum use rate, total usage of indole would not exceed 6.7 grams per acre.

Guideline toxicity and non-target organism studies were not submitted in support of the registrant's application. In lieu of studies, the registrant requested data waivers from the requirements for all guideline studies and submitted a compendium of information in support of the data waivers. The registrant also provided adequate justification for waiving data requirements based on the proposed use pattern, which would result in no exposure to the active ingredient. Therefore, the Agency believes that this product containing indole can be used without causing unreasonable adverse effects to humans or the environment.

Based on data and acceptable waivers submitted by the registrant, there is no reason to believe that any non-target organisms, including honeybees and other beneficial insects, would be attracted to or adversely affected by the use of indole in a fly trap. Data submitted by the registrant indicated that only insects classified as "filth flies" were attracted to the fly trap.

Due to the negligible risk concerns when used as an attractant and the resulting lack of exposure, indole meets the criteria as specified in §3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, and is thus eligible for unconditional registration. It was determined that the data/information submitted adequately satisfy current guideline requirements per 40 CFR Subpart U §158.2000.

II. ACTIVE INGREDIENT OVERVIEW

Common Name: Indole

Chemical Names: Indole

Trade & Other Names: 1-Azaindene
1-Benzazole
1-Benzo(b)pyrrole,
2,3-Benzopyrole
2,3-Benzopyrrole
Indol
Ketole

CAS Registry Number: 120-72-9

OPP Chemical Code: 025000

Type of Pesticide: Biochemical pesticide, attractant

Application rates and methods vary depending on the product. For specific information regarding the product*(s)* refer to Appendix B.

III. REGULATORY BACKGROUND

On April 4, 2008, the Agency received an application from Bull Run Scientific, VBT to register indole as an active ingredient in an end-use product (EP) containing 0.2% indole. A notice of receipt of the application for registration for trimethylamine as a new active ingredient was published in the Federal Register on March 11, 2009, with a 30 day comment period. No comments were received as a result of this publication.

A. Classification

On September 1, 1993, the Biochemical Classification Committee determined that indole can be classified as a biochemical pesticide due to its non-toxic mode of action, natural occurrence in the environment, and history of exposure to humans and the environment demonstrating minimal toxicity at low concentrations. In a concentrated form, indole can be both toxic and a sensory irritant. Used in Biochemical pesticides at low concentrations as an attractant, however, it demonstrates minimal toxicity.

B. Food Clearances/Tolerances

Currently, this active ingredient is not registered for use on food or feed commodities. A tolerance or exemption from the requirement of a tolerance is not relevant.

IV. RISK ASSESSMENT

A. Active Ingredient Characterization

The new active ingredient, indole, will be formulated as an EP for use as an attractant for filth flies. The technical grade active ingredient (TGAI) is a flaky white solid. It has the odor of feces at high concentrations but, at lower concentrations, has a flowery scent. In its pure form, indole is toxic with an LD_{50} of 1000mg/kg.

The mode of action of indole is to produce odors that attract filth flies seeking a food source or medium in which to deposit their eggs. As part of a water-soluble attractant insert in a disposable or re-useable trap, it draws filth flies into the apparatus where they are trapped.

The product chemistry data submitted by the registrant, including manufacturing process, discussion of formation of impurities, analysis of samples, and certified ingredients limits satisfied the requirement for product identity. Refer to Table 1 in Appendix A for a summary of product chemistry data requirements. Refer to Table 2 in Appendix A for the summary of physical and chemical characteristics for indole.

All product chemistry data requirements for registration of indole have been **satisfied.**

B. Human Health Assessment

1. Toxicology

For acute toxicity data requirements, toxicity categories are assigned based on the hazard(s) identified from studies and/or information on file with the Agency. The active ingredient is classified into Toxicity Category I, II, III or IV where Toxicity Category I indicates the highest toxicity and Toxicity Category IV indicates the lowest toxicity. For more information, refer to 40 CFR § 156.62.

Adequate mammalian toxicology data/information is available to support registration of indole. All toxicology data requirements for indole have been **satisfied.**

a. Acute Toxicity

Acute toxicity testing is required to 1) determine systemic toxicity from acute exposure via the dermal, inhalation and oral routes, 2) determine irritant effects from exposure to the eyes and 3) determine the potential for skin sensitization (allergic contact dermatitis). All required toxicology data for indole are waived. No additional toxicological data are needed. The decision to waive these data is based on: 1) the product is naturally occurring, 2) possesses a non-toxic mode of action, 3) will not accumulate in the environment, and 4) due to the design of

the trap, there is no anticipated exposure to the attractant pouch ingredients. For more information regarding the acute toxicity data requirements, refer to Table 3 in Appendix A.

b. Subchronic Toxicity

Subchronic data is required to determine a no-observed-effect-level (NOEL) and toxic effects (if any) associated with repeated or continuous exposure to a test substance for a period of 90 days. The request submitted by the registrant to waive subchronic mammalian toxicity data was determined to be acceptable. For more information regarding the subchronic data requirements, refer to Table 3 in Appendix A.

c. Developmental Toxicity and Mutagenicity

The Agency waived data requirements for developmental toxicity and mutagenicity of indole based on 1) its natural occurrence in the environment, 2) little to no potential for exposure to humans based on the EP attractant packet and fly trap designs and 3) the fact that it will not accumulate in the environment. For more information regarding these data requirements, refer to Table 3 in Appendix A.

e. Effects on the Endocrine System

EPA is required under the Federal Food, Drug, and Cosmetics Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the program include evaluations of potential effects in wildlife. For pesticide chemicals, the Agency will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

The Agency is not requiring information on the endocrine effects of indole at this time. The Agency has considered, among other relevant factors, available information concerning whether the active ingredient may have an effect on humans similar to an effect produced by naturally-occurring estrogen or other endocrine effects. There is no known metabolite that acts as an endocrine disrupter produced by this active ingredient. Based on the low potential exposure level associated with the proposed use, the Agency expects no incremental adverse effects to the endocrine or immune systems.

2. Dose Response Assessment

No toxicological endpoints were identified; therefore, a dose response assessment was not required.

3. Drinking Water Exposure and Risk Characterization

Based on the proposed use pattern, no significant exposure is expected from use of indole in the environment when used according to label instructions.

4. Occupational, Residential, School and Day Care Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

Occupational exposures are not a concern based on the use pattern, low to no potential for exposure due to trap design, and because indole is naturally occurring in the environment and possesses a non-toxic mode of action when used as an attractant at a low concentration. The application method of indole inside a water-soluble pouch that is placed within a trap poses no significant concern for dermal, eye, and inhalation exposures. Based on little or no potential for exposure and the small percentage of indole in the attractant pouch, worker exposure data on indole are not required. Based on the nature, use pattern, non-toxic mode of action, and relative safety of indole in this product, including the battery of information from the open scientific literature, the toxicity category for the fly attractant has been characterized as IV and the product label will bear the signal word "Caution." No reentry interval is required in conjunction with the use of the EP.

b. Residential, School and Day Care Exposure and Risk Characterization

The end use product containing indole is intended for use in a residential or agricultural setting. Again, because indole is naturally occurring, possesses a non-toxic mode of action, and the trap design will result in low potential for exposure, the Agency is not concerned about the potential exposure to children.

5. Risk Characterization

The Agency considered human exposure to indole in light of the relevant safety factors in FIFRA. A determination has been made that no unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, will result from the use of indole when label instructions are followed.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Hazards

Based on the natural occurrence of indole as a component of animal feces and the fact that indole is not expected to cause adverse effects on non-target organisms, adequate rationales for waiving non-target toxicology data were submitted to support registration of indole. All non-target toxicology data requirements for indole have been **satisfied.**

For more information regarding the non-target toxicity data requirements, refer to Table 4 in Appendix A.

2. Environmental Fate and Ground Water Data

The need for environmental fate and groundwater data was not triggered because results of the acute toxicity studies did not trigger any additional Tier I studies.

3. Ecological Exposure and Risk Characterization

The end use product, Bull Run Fly Attractant, is intended for residential or agricultural use. When used according to the proposed label directions, no direct exposures are expected for non-target organisms. Moreover, the active ingredient is naturally occurring, has a non-toxic mode of action when used at a low concentration as an attractant, is a natural component of feces, and is not expected to accumulate in the environment. Given these characteristics of indole, non-target exposure and ecological effects studies were waived for the use of indole in the fly trap.

4. Endangered Species Assessment

Adverse effects on threatened and endangered species are not expected based on available information about the use pattern of the product, product performance data, and habitat of Diptera species currently listed as threatened or endangered.

D. PRODUCT PERFORMANCE DATA (EFFICACY)

Submission of product performance data (OPPTS 810.3000) is listed as a requirement for all pesticide products. Customarily, the Agency requires efficacy data to be submitted for review only in connection with the registration of products directly pertaining to the mitigation of disease bearing human health organisms and certain designated quarantine pests, i.e., ticks, mosquitoes, fleas, Mediterranean fruit flies, gypsy moths, Japanese beetles, etc. For a list of organisms considered by the Agency as “public health pests”, please refer to Pesticide Registration Notice 2002-1 (http://www.epa.gov/PR_Notices/pr2002-1.pdf).

Based on the data submitted by the registrant, the Agency determined that product performance data were acceptable.

V. Risk Management Decision

A. Determination of Eligibility for Registration

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the environment; and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

The four criteria of the Eligibility Determination for Pesticidal Active Ingredients are satisfied by the science assessments supporting products containing indole. Such products are not expected to cause unreasonable adverse effects, and are likely to provide protection as claimed when used according to label instructions. Therefore, indole is eligible for registration for the labeled uses.

B. Regulatory Decision

The data submitted fulfill the requirements of registration for use as an ingredient in a water-soluble, vapor-barrier fly attractant packet inside an insect trap. Refer to Appendix B for product-specific information.

1. Conditional/Unconditional Registration

All data requirements are fulfilled and EPA has determined that unconditional registration of indole is appropriate.

C. Environmental Justice

EPA seeks to achieve environmental justice - the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income - in the development, implementation, and enforcement of environmental laws, regulations, and policies. At this time EPA does not believe that use of pesticide products containing indole will cause harm or a disproportionate impact on at-risk communities.

For additional information regarding environmental justice issues, please visit EPA's website at: http://www.epa.gov/compliance/environmentaljustice/index.html.

VI. ACTIONS REQUIRED BY REGISTRANTS

The Agency evaluated all of the data submitted in connection with the initial registration of indole and determined that these data are sufficient to satisfy current registration data requirements. No additional data are required to be submitted to the Agency at this time. For new uses and/or changes to existing uses, additional data may be required.

Not withstanding the information stated in the previous paragraph, it should be clearly understood that certain, specific, data are required to be reported to the Agency as a requirement for maintaining the Federal registration for a pesticide product. A brief summary of these types of data are listed below.

A. Reporting of Adverse Effects

Reports of all incidents of adverse effects to the environment must be submitted to the Agency under the provisions stated in FIFRA, Section 6(a)(2).

B. Reporting of Hypersensitivity Incidents

Additionally, all incidents of hypersensitivity (including both suspected and confirmed incidents) must be reported to the Agency under the provisions of 40 CFR Part 158.2050(d).

VII. Appendix A. Data Requirements (40 CFR Part 158-Subpart U)

*NOTE: MRID numbers listed in the following tables are representative of supporting data for the original registration of the product containing this active ingredient. Subsequent to this registration, there may be additional MRIDs that support registration of other products containing this active ingredient.

TABLE 1. Product Chemistry Data Requirements for Indole (40 CFR § 158.2030)

OPPTS Guideline No.	Study	Results	MRID
830.1550 to 830.1670	Product identity; Manufacturing process; Discussion of formation of unintentional ingredients	Submitted data satisfy the requirements for product identity, manufacturing process, and discussion of formation of impurities.	473969-16
830.1700	Analysis of samples	Submitted data satisfy the requirements for analysis of samples.	473969-16
830.1750	Certification of limits	Limits listed in the CSF are adequate / acceptable.	473969-16
830.1800	Analytical method	Acceptable.	473969-16

TABLE 2. Physical and Chemical Properties of Indole (40 CFR § 158.2030)

OPPTS Guideline No.	Property	Description of Result	MRID
830.6302	Color	White	473969-17
830.6303	Physical State	Solid at room temperature	473969-17
830.6304	Odor	Fecal odor at high concentration, flowery odor at low concentration	473969-17
830.6313	Stability to Normal and Elevated Temperatures, Metals and Metal Ions	Stable for 12 months when stored in original package, tightly sealed in cool, dry location.	473969-17
830.6315	Flammability	Not required for EP	N/A
830.6317	Storage Stability	Stable for 12 months	473969-17
830.6319	Miscibility	Not required for EP	N/A
830.6320	Corrosion Characteristics	Not required for EP	N/A
830.7000	pH	5.9	473969-18
830.7050	UV/Visible Light Absorption	Not required for EP	N/A
830.7100	Viscosity	Not applicable	N/A
830.7200	Melting Point/Range	52.5°C	473969-17
830.7220	Boiling Point/Range	254°C	473969-17
830.7300	Density	1.22 g/cm^3	473969-17
830.7520	Particle Size, Fiber Length and Diameter Distribution	Not required for EP	N/A
830.7550 830.7560 830.7570	Partition Coefficient (n-Octanol/Water)	Log Kow = 2.14	473969-17
830.7840	Water Solubility	3560 mg/L at 25°C	473969-17
830.7950	Vapor Pressure	0.0122 mm Hg at 25°C	473969-17

Table 3. Human Toxicology Data Requirements for Indole (40 CFR § 158.2050)			
Study/OPPTS Guideline No.	**Results**	**Toxicity Category/Description**	**MRID**
Acute oral toxicity (rat) (870.1100)	Waiver requested*	Acceptable	473969-21
Acute dermal toxicity (rat) (870.1200)	Waiver requested*	Acceptable	473969-21
Acute inhalation toxicity (rat) (870.1300)	Waiver requested*	Acceptable	473969-21
Primary eye irritation (rabbit) (870.2400)	Waiver requested*	Acceptable	473969-21
Primary dermal irritation (rabbit) (870.2500)	Waiver requested*	Acceptable	473969-21
Dermal sensitization (guinea pig) (870.2600)	Waiver requested*	Acceptable	473969-21
Hypersensitivity incidents (885.3400)	Waiver requested*	Acceptable	473969-21
90-Day oral toxicity (870.3100)	Waived due to lack of exposure	N/A	
90-Day dermal toxicity (870.3250)	Waived due to lack of exposure	N/A	
90-Day inhalation toxicity (870.3465)	Waived due to lack of exposure	N/A	
Mutagenicity (870.5100, 5300 and 5375)	Waived due to lack of exposure	N/A	
Developmental toxicity (870.3700)	Waived due to lack of exposure	N/A	

* Due to the fact that no significant human exposure is expected, the Agency did not require human health data on the Technical Grade Active Ingredient (TGAI). This is due to the fact that the active ingredient is enclosed in a water-soluble vapor barrier packet which is placed inside the fly trap, resulting in no exposure to the product handler. The Agency did, however, require data for the EP.

TABLE 4. Non-Target Organism Toxicity Requirements for Indole (40 CFR § 158.2060)			
Study/OPPTS Guideline No. /MRID No.	**Results**	**Toxicity Category/Description**	**MRID**
Avian acute oral toxicity *Colinus virginianus* (850.2100)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Avian dietary toxicity *Colinus virginianus* (850.2200)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Avian dietary toxicity *Anas platyrhynchos* (850.2200)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Aquatic invertebrate acute toxicity (*Daphnia magna*) (850.1010)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Freshwater fish LC_{50} (*Oncorhynchus mykiss*) (850.1075)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Non-target plant studies (850.4000-4800, as applicable)	Waived only for the proposed use pattern of the EP contained within a water-soluble vapor barrier packet inside the fly trap	Acceptable	473969-20
Non-target insect testing (880.4350)	The study, Product performance data indicated no evidence that the product attracts non-target insects.	Acceptable	473696-03

VIII. Appendix B.

For product specific information, please refer to http://www.epa.gov/pesticides/pestlabels/

IX. Appendix C.

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