BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Refined Oil of *Nepeta cataria*
[Hydrogenated Catmint Oil (HCO)]

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

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This document is for informational purposes only and is representative of the Agency's justification in registering products containing this active ingredient. This is not a legal document. (Need OGC language)

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I. EXECUTIVE SUMMARY:

The active ingredient is a refined, multi-component extract of oil *Nepeta cataria* which is a member of the mint family of plants (*Labiatae*). The technical grade active ingredient (TGAI) is identified as Refined Oil of *Nepeta cataria* and is also referred to as Hydrogenated Catmint Oil (HCO). The technical grade active ingredient is intended for use in the manufacture of a dermally applied insect repellent for direct application to human skin to repel black flies, mosquitoes and other biting insects.

The Biopesticides and Pollution Prevention Division (BPPD) has determined that the data/information submitted for Tier I Acute Toxicity and Product Chemistry adequately satisfy current guideline requirements (refer to 40 CFR Subpart U § 158.2000). Non-target toxicology data requirement were satisfied by the submission of data waivers for non-target organism granted by BPPD based on the low quantity of Refined Oil of *Nepeta cataria*, limited breadth of application and low hazards to non-target species presented in the scientific literature and rationale for the proposed use of Refined Oil of *Nepeta cataria* as an insect repellent. This will preclude significant adverse exposure and risk to non-target organisms. Based on the information discussed above, the Agency has determined that Technical Grade of Refined Oil of *Nepeta cataria* as an active ingredient will have **No Adverse Effects (NAE)** on threatened and/or endangered species.

Based on the Acute Toxicity and Product Chemistry data available to the Agency, the technical grade active ingredient is classified into Toxicity Category III for oral toxicity and primary eye irritation and Toxicity Category IV for dermal, inhalation and skin irritation. The Agency has determined that no unreasonable adverse effects to the U.S. population will result from the use of the active ingredient when label instructions are followed. There are no reports of adverse effects following regular human exposure and consumption of Refined Oil of *Nepeta cataria*. Moreover, the pesticidal usage of this biochemical will not have any harmful environmental effects.

The Biopesticides and Pollution Prevention Division (BPPD) has reviewed data /information in support of the requirements for granting registration under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). It was determined that the data/information submitted adequately satisfy current guideline requirements (refer to 40 CFR Subpart U § 158.2000).

II. ACTIVE INGREDIENT OVERVIEW

Common Name: Hydrogenated catmint oil (HCO)

Chemical Names: Refined Oil of *Nepeta cataria*

Trade & Other Names: Hydrogenated *Nepeta cataria* Oil

CAS Registry Number: 952722-18-8

OPP Chemical Code: 004801

Type of Pesticide: Biochemical pesticide (Insect Repellent)

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

III. REGULATORY BACKGROUND

Dupont Chemical Solutions Enterprise submitted an application for the registration of a new biochemical pesticide Technical (TGAI), containing the active ingredient Refined Oil of *Nepeta cataria* on October 12, 2006**.** A notice of receipt of an application for registration of Refined Oil of *Nepeta cataria* as an active ingredient, was published in the Federal Register on February 27, 2008 (73 FR 10434-35) with a 30-day comment period. No comments were received following this publication.

A. Classification

On February 27, 2006, the Biochemical Classification Committee determined that Refined Oil of *Nepeta cataria* qualified to be reviewed in BPPD for a reduced data set. The classification is based on the active ingredient being derived from a natural and botanical source, its low toxicity, and its use as a medicinal and nutritional ingredient for humans.

B. Food Clearances/Tolerances

Currently, this active ingredient is proposed for non food or feed uses.

IV. RISK ASSESSMENT

A. Active Ingredient Characterization

The active ingredient is a refined, multi-component extract of *Nepeta cataria* which is a member of the mint family of plants (*Labiatae*). The technical grade active ingredient (TGAI) is identified on proposed product labels as Refined Oil of *Nepeta cataria* and is also referred to as Hydrogenated Catmint Oil (HCO). The plant is commonly known as catnip and is indigenous from eastern Mediterranean to eastern Himalayan regions. The perennial herb can also be grown in North America. General information on the nature of the active ingredient is readily available (e.g., http://chemistry.about.com/library/weekly/aa103001a.htm; accessed on October 2, 2007) and is summarized as background information below.

Nepetalactone is the major component of the refined oil, but there are other components such as puleganic acid with known insect repellent activity. Nepetalactone is a terpene comprised of two isoprene units, and it has a chemical structure similar to that of the valepotriates (from the herb valerian) which have mild central nervous system effects in humans (sedative or stimulant depending on the individual).

Historically, oil of *Nepeta cataria* has been used in herbal medicine to treat fever, head and tooth aches, colds, colic and spasms in humans. In some individuals catnip can be used to induce sleep, but it can also act as a stimulant in others. At high doses it is emetic in cats and humans. Other historical uses included rubbing meat with catnip leaves, adding it to salads or making tea with it. The principal insect repellent components in Refined Oil of *Nepeta cataria* are dihydronepetalactone (69.99% w/w) and puleganic acid (6.77% w/w).

The description of the production process on the technical (TGAI), as well as the formation of impurities, were examined by the Agency and found to be acceptable in meeting current guideline standards. The analytical method used to determine the content of the active ingredient is also acceptable. Physical and chemical properties were submitted for the technical grade active ingredient and are adequate. 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 technical grade Refined Oil of *Nepeta cataria.*

All product chemistry data requirements for registration of Refined Oil of *Nepeta cataria* as the TGAI 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 http://www.epa.gov/pesticides/pestlabels/ .

Technical grade Refined Oil of *Nepeta cataria* is classified into Toxicity Category III for oral toxicity and primary eye irritation and Toxicity Category IV for dermal, inhalation and skin irritation. It is not a skin sensitizer.

The registrant submitted a discussion (MRID 47362604) that addressed the questions EPA had regarding a positive mouse lymphoma assay. The discussion provided an acceptable rationale for the TGAI being non-genotoxic and explores the concept of false test positives and weight of the evidence.

Adequate mammalian toxicology data/information is available to support registration of the technical grade active ingredient, Refined Oil of *Nepeta cataria*. All toxicology data requirements for the technical grade active ingredient (TGAI) have been **satisfied.**

a. Acute Toxicity

Acute toxicity studies submitted in support of the technical grade active ingredient, Refined Oil of *Nepeta cataria* are summarized in Table 3 in Appendix A. Refined Oil of *Nepeta cataria* is classified in Toxicity Category III for acute oral toxicity and primary eye irritation and Toxicity Category IV for acute dermal, acute inhalation and skin irritation. It is not a dermal sensitizer. Based on the review and analysis of the information, guideline studies, and submitted literature discussed in detail in this section of the BRAD, no additional toxicity data are required to support the non food use of this of this active ingredient.

b. Subchronic Toxicity

In an acceptable oral toxicity study (MRID 46977407), hydrogenated catmint oil (HCO) was administered by gavages daily to groups of ten rats/sex at doses of 0, 40, 200, and 1000 mg/kg body weight for 93 days. Hematological, clinical chemistry, urinalysis, opthalmoscopic, neurological, and microscopic tissue and organ effects were determined only in the subchronic studies. All rats in the study survived until scheduled sacrifice. The only persistent clinical observation reported was perineal staining throughout the study on three female high-dose rats. No neurological or opthalmoscopic effects were noted. The subchronic oral toxicity study in rats demonstrated a no-observed-effect level (NOEL) of 200 mg/kg/day and a lowest-observable-effect level (LOEL) of 1000 mg/kg/day based on the increased incidence of minimal to mild degeneration/regeneration of the olfactory epithelium lining the nasal turbanates of treated male and female rats. No systemic toxicity was observed in the subchronic dermal toxicity study at dose levels up to 1000 mg/kg/day.

c. Developmental Toxicity and Mutagenicity

There were no adverse effects observed in a 28-day oral immunotoxicity study or in a developmental toxicity study at oral doses up to 1000 mg/kg/day. No genetic toxicity was observed in bacteria (point mutation assay), an in vitro cytogenetics assay, or in a mouse micronucleus assay. However, a point mutation assay in mouse lymphoma cells reported an increased frequency of point mutations at doses approaching cytotoxic levels without metabolic activation. The registrant submitted a discussion (MRID 47362604) that addressed the questions EPA had regarding a positive mouse lymphoma assay. The discussion provided an acceptable rationale for the TGAI being non-genotoxic and explores the concept of false test positives and weight of the evidence.

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 Refined Oil of *Nepeta cataria* 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 of the end use products, 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

No significant exposure via drinking water is expected when Refined Oil of *Nepeta cataria* is used according to the product label directions. The technical grade active ingredient is intended for use in the manufacture of a dermally applied insect repellent for direct application to human skin and not to be applied directly to water or to areas where surface water is present, and if used as labeled, is not likely to accumulate in drinking water. In the unlikely event that exposure via drinking water did occur, the health risk would be expected to be minimal, based on the low acute oral and dermal toxicity of Refined Oil of *Nepeta cataria.*

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

a. Occupational Exposure and Risk Characterization

No occupational estimates are made in this assessment since Refined Oil of *Nepeta cataria* is to be used by individuals as an insect repellent that they apply directly to their own skin. Non-occupational dermal exposure estimates were not determined because the subchronic dermal toxicity study did not demonstrate an endpoint for use in risk characterization, human skin is much less permeable to Refined Oil of *Nepeta cataria* than rat skin (MRID 47015601), and the label indicates that advice from a physician or Poison Control Center should be sought when reactions to exposure from use of the products are suspected. Again, the directions for use on the proposed end use labels indicated that application of the lotions or liquid sprays to children's fingers and hands was to be avoided. Therefore, no exposure estimates were determined for incidental oral exposure.

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

Since the technical grade active ingredient is intended for use in the manufacture of a dermal applied insect repellent for direct application to human skin, significant human exposure to Refined Oil of *Nepeta cataria* will be minimal in residential, school and day care areas when the end use product is used according to the label directions. The acute neurotoxicity endpoint is appropriate to an incidental oral exposure for children, but because the effect is reversible and pharmacological in nature (reduced activity) and the label contains instructions to avoid incidental exposure (i.e., licking of fingers and hands), no risk characterization was done for incidental oral scenarios. Should accidental exposure occur, the health risk is expected to be minimal, based on the low acute oral, dermal, and inhalation toxicity of Refined Oil of *Nepeta cataria*.

5. Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation

There is reasonable certainty that no harm to the US population will result from aggregate exposure to Refined Oil of *Nepeta cataria.*. The Agency arrived at this conclusion based on the low level of toxicity of Refined Oil of *Nepeta cataria* as a food ingredient by the general public without any reported adverse effects on human health. The risks from aggregate exposure via oral, dermal and inhalation exposure are a compilation of three low-risk exposure scenarios and are negligible. Since there are no threshold effects of concern, the provision requiring an additional margin of safety does not apply. Therefore, the Agency has not used a margin of exposure (safety) approach to assess the safety of Refined Oil of *Nepeta cataria.*

6. Cumulative Effects

Based on the information available to the Agency, there is no indication that toxic effects associated with exposure to Refined Oil of *Nepeta cataria* are of toxicological concern. Because the technical grade active ingredient's low toxicity, cumulative effects with other substances that share a common mechanism of toxicity are not expected.

7. Risk Characterization

The Agency considered human exposure to Refined Oil of *Nepeta cataria* in light of the relevant safety factors in FQPA and 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 Refined Oil of *Nepeta cataria* when label instructions are followed.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Hazards

Ecological effects data requirements for technical grade Refined Oil of *Nepeta cataria* were satisfied by the submission of data waiver requests pertaining to effects on Non-Target organisms. Based on the waiver rationale, the Agency concluded that exposure and risk from the

proposed use of the manufacture and integration of the technical grade Refined Oil of *Nepeta cataria* into a formulated product is not expected to occur or pose a threat to non-target organisms. Since the active ingredient is a technical grade product, non-target requirements can be waived by the submissions of data waivers which will be a condition of the registration.

2. Environmental Fate and Ground Water Data

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

3. Ecological Exposure and Risk Characterization

Based on the rationales submitted in the data waiver requests, exposure and risk from the proposed use of the manufacture and integration of the technical grade Refined Oil of *Nepeta cataria* into a formulated product is not expected to occur for non-target organisms.

4. Endangered Species Assessment

Based on the information discussed above, the Agency has determined that registered use of Refined Oil of *Nepeta cataria* as an active ingredient will have **No Adverse Effects (NAE)** on threatened and/or endangered species. When the product is used according to label use directions, there are no concerns for any non-target organisms.

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 Refined Oil of *Nepeta cataria*. 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, Refined Oil of *Nepeta cataria* is eligible for registration for the labeled uses.

B. Regulatory Decision

The data submitted fulfill the requirements of registration for use of Refined Oil of *Nepeta cataria* for use in the manufacture of a dermally applied insect repellent for direct application to human skin to repel black flies, mosquitoes and other biting insects. 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 technical grade Refined Oil of *Nepeta cataria* 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. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to Refined Oil of *Nepeta cataria*, compared to the general population. Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.

VI. ACTIONS REQUIRED BY REGISTRANTS

The Agency evaluated all of the data submitted in connection with the initial registration of technical grade Refined Oil of *Nepeta cataria* 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 Refined Oil of *Nepeta cataria* (40 CFR § 158.2030)

OPPTS Guideline No.	Study	Results *(below are example results)*
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.
830.1700	Analysis of samples	Submitted data satisfy the requirements for analysis of samples.
830.1750	Certification of limits	Limits listed in the CSF are adequate / acceptable.
830.1800	Analytical method	Acceptable.

TABLE 2. Physical and Chemical Properties of Refined Oil of *Nepeta cataria* (40 CFR § 158.2030)

OPPTS Guideline No.	Property	Description of Result
830.6302	Color	Yellow @ 21ºC
830.6303	Physical State	Liquid @ 21ºC
830.6304	Odor	Minty
830.6313	Stability to Normal and Elevated Temperatures, Metals and Metal Ions	Stable at room and elevated temperatures and in the presence of metals and ions.
830.6314	Oxidation/Reduction: Chemical Incompatibility	Dihydronepetalactone was relatively stable in solution with metals and metal salts after 14 days at 25ºC, with slight decreases at 54ºC after 14 days.
830.6315	Flammability	>99ºC
830.6317	Storage Stability	In short-term testing at 25 and 54ºC, dihydronepetalactone content was relatively stable. Guideline study is in progress.
830.6319	Miscibility	Not applicable, product is not to be diluted in petroleum solvents
830.6320	Corrosion Characteristics	Guideline study is in progress
830.7000	pH	3.97 @ 25ºC (1% w/w in deionized water)
830.7050	UV/Visible Light Absorption	Not applicable
830.7100	Viscosity	18.09 mm^2/s (cSt) @ 22ºC
830.7200	Melting Point/Range	Not applicable, product is a liquid
830.7220	Boiling Point/Range	266.0 ± 12.0ºC
830.7300	Density	1.0334 @ 20.7ºC
830.7520	Particle Size, Fiber Length and Diameter Distribution	
830.7550 830.7560 830.7570	Partition Coefficient (n-Octanol/Water)	Not applicable, required only for pure active ingredient
830.7840	Water Solubility	0.254 ± 0.013 g/L @ 30ºC
830.7950	Vapor Pressure	591, 707, 907. 1100, 1320, and 1630 Pa @ 20, 25, 30, 35, and 40ºC, respectively

Table 3. Human Toxicology Data Requirements for Refined Oil of Refined Oil of *Nepeta cataria* (40 CFR § 158.2050)		
Study/OPPTS Guideline No.	**Results**	**Toxicity Category/Description**
Acute oral toxicity (rat) (870.1100)	LD_{50} = 1750 (95% C.L. 455.5-9230) mg/kg (females using the Up-and Down Method)	**III** / MRID 46977401
Acute dermal toxicity (rat) (870.1200)	LD_{50} > 5000 mg/kg for males, females, and for both sexes combined.	**IV** / MRID 46977402
Acute inhalation toxicity (rat) (870.1300)	LC_{50} > 5.5 mg/L (males, females, and both sexes combined; 4 hour nose-only exposure)	**IV** / MRID 46977406
Primary eye irritation (rabbit) (870.2400)	Corneal opacity persisted for 24 to 48 hours after treatment with clearance by 72 hours. Iritis was noted at 1 and 24 hours after treatment and cleared by the 48 hour observation. Conjunctival irritation was noted on one rabbit one hour throughout 48 hours after treatment with clearance by 72 hours. The maximum average score was 24.0 at 24 hours after test material instillation. Hydrogenated Catmint Oil was mildly irritating.	**III** / MRID 46977403
Primary dermal irritation (rabbit) (870.2500)	No dermal irritation or clinical signs of toxicity were observed during the study. The primary irritation index was 0.0.	**IV** / MRID 46977404
Dermal sensitization (mouse) (870.2600)	A local lymph node assay (LLNA) indicated that hydrogenated catmint oil is not a dermal sensitizer.	--- / MRID 46977405
90-Day oral toxicity (rat) (870.3100)	Minimal to mild degeneration / regeneration of the olfactory epithelium lining the nasal turbinates of males and females. **NOAEL** = 200 mg/kg **LOAEL** = 1000 mg/kg	MRID 46977407
90-Day dermal toxicity (rat) (870.3250)	No adverse effects were reported. **NOAEL** = 1000 mg/kg **LOAEL** > 1000 mg/kg	MRID 46977415
Mutagenicity (Bateria) (870.5100, 5300 and 5375)	Negative **Doses tested:**0 to 5000 µg/plate with or without metabolic activation (S9 mix)	MRID 46977410
Developmental toxicity (rat) (870.3700)	No adverse effects were reported. **NOAEL** = 1000 mg/kg **LOAEL** > 1000 mg/kg	MRID 46977408

TABLE 4. Non-Target Organism Toxicity Requirements for Refined Oil of *Nepeta cataria* (40 CFR § 158.2060)		
Study/OPPTS Guideline No.	**Results**	**Toxicity Category/Description**
Avian acute oral toxicity *Colinus virginianus* (850.2100)	**Data Waiver Request submitted**	
Avian dietary toxicity *Colinus virginianus* (850.2200)	**Data Waiver Request submitted**	
Avian dietary toxicity *Anas platyrhynchos* (850.2200)	**Data Waiver Request submitted**	
Aquatic invertebrate acute toxicity (*Daphnia magna*) (850.1010)	**Data Waiver Request submitted**	
Freshwater fish LC_{50} (*Oncorhynchus mykiss*) (850.1075)	**Data Waiver Request submitted**	
Non-target plant studies (850.4000-4800, as applicable)	**Data Waiver Request submitted**	
Non-target insect testing (880.4350)	**Data Waiver Request submitted**	

VIII. Appendix B.

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

IX. Appendix C.

REFERENCES