



BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Cold Pressed Neem Oil
PC Code 025006

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

(Last updated May 7, 2012)

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.

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY	5
II. ACTIVE INGREDIENT OVERVIEW.....	6
III. REGULATORY BACKGROUND.....	6
A. Classification	7
B. Food Clearances/Tolerances	7
IV. RISK ASSESSMENT	7
A. Active Ingredient Characterization.....	7
B. Human Health Assessment.....	8
1. Toxicology.....	8
a. Acute Toxicity.....	8
b. Sub-chronic Toxicity	8
c. Developmental Toxicity and Mutagenicity.....	9
d. Effects on the Endocrine System.....	9
2. Dose Response Assessment.....	10
3. Food Quality Protection Act (FQPA) Consideration.....	10
a. Dietary Exposure and Risk Characterization.....	10
b. Drinking Water Exposure and Risk Characterization.....	10
c. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children.....	11
4. Occupational, Residential, School and Day Care Exposure and Risk Characterization.....	11
a. Occupational Exposure and Risk Characterization.....	11
b. Residential, School and Day Care Exposure and Risk Characterization	11
5. Cumulative Effects.....	12
6. Risk Characterization.....	12
C. Environmental Assessment.....	12
1. Ecological Hazards	12
2. Environmental Fate and Ground Water Data.....	12
3. Ecological Exposure and Risk Characterization.....	13
4. Endangered Species Assessment	13
D. Product Performance (Efficacy)	13
V. RISK MANAGEMENT DECISION.....	14
A. Determination of Eligibility for Registration.....	14

B. Regulatory Decision.....14

C. Environmental Justice15

VI. ACTIONS REQUIRED BY REGISTRANTS 15

A. Reporting of Adverse Effects15

B. Reporting of Hypersensitivity Incidents15

VII. APPENDIX A 16

VIII. APPENDIX B..... 19

IX. APPENDIX C 20

BIOPESTICIDES REGISTRATION ACTION DOCUMENT TEAM

Office of Pesticide Programs

Biopesticides and Pollution Prevention Division

Biochemical Pesticides Branch:

Driss Benmhend	Regulatory Action Leader
Gina Burnett, M.S.	Regulatory Action Leader
Linda Hollis, M.S.	Branch Chief
Jacob Moore	Chemist
Manying Xue, M.S	Chemist
Clara Fuentes, Ph.D.	Entomologist
Russell Jones, Ph.D.	Senior Biologist

I. EXECUTIVE SUMMARY

The active ingredient Cold Pressed Neem Oil is pressed directly from seeds of the Neem tree (*Azadirachta indica*), which is a tropical evergreen tree native to India and also found in other Southeast Asian and African countries. Cold Pressed Neem Oil has a brown color, a bitter taste and a garlic/sulfur smell. Cold pressed Neem Oil has demonstrated properties as an insect repellent, insect growth regulator, and insecticide.

In October 2009, the Biopesticides and Pollution Prevention Division (BPPD) reviewed data required to support the registration of this biochemical active ingredient, under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), for use on outdoor and greenhouse agricultural food and ornamental crops. At that time, product chemistry data requirements were satisfied by acceptable guideline studies. Adequate mammalian toxicology data/information was submitted to support registration of Cold Pressed Neem Oil for outdoor uses on crops and ornamentals. Specifically, acceptable acute toxicity guideline studies were submitted, and data waivers were granted by the Agency for the remaining toxicity requirements based on the lack of toxicity of the active ingredient. Ecological effects data requirements for Cold Pressed Neem Oil were fulfilled by acceptable guideline studies and additional data/information from the scientific literature sufficient to support the remaining Tier I and Tier II requirements.

In March 2012, BPPD reviewed data required to support the addition of a “new use” to the Cold Pressed Neem Oil registration. The “new use” is indoor use for the control of bed bugs. In support of this use, additional mammalian toxicology data/information was submitted to fulfill the biochemical pesticide data requirements of 90-day dermal toxicity and 90-day inhalation toxicity. Product performance (efficacy data) was submitted to support label claims.

Based on the data available to the Agency, it has been determined that no unreasonable adverse effects to the U.S. population and the environment will result from the use of the active ingredient when label instructions are followed and good agricultural practices are employed. Laboratory studies indicate that the active ingredient is not toxic following oral, inhalation or dermal exposure. Cold Pressed Neem Oil and neem extracts are widely used in cosmetics (soap, hair products, hand creams, etc.), traditional folk medicine (acne, fevers, rheumatism, diuretics, inflammations, etc.), as an insect repellent, insecticide, nematicide, fungicide, and as a fertilizer. There are no reports of adverse effects following human exposure to this biochemical. Moreover, the pesticidal usage of Cold Pressed Neem Oil will not have any harmful environmental effects. Studies indicate that Cold Pressed Neem Oil will not cause adverse effects to mammals, birds, fish and aquatic invertebrates, other non-target insects, or plants.

Due to the negligible risk concerns when used as an insect repellent, insect growth regulator, and insecticide, Cold Pressed Neem Oil 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 applicable data requirements at 40 C.F.R. Subpart U §158.2000.

II. ACTIVE INGREDIENT OVERVIEW

Common Name: Neem Oil

Chemical Names: Cold Pressed Neem Oil

Trade & Other Names: Cold Pressed Neem Oil

CAS Registry Number: 8002-65-1

OPP Chemical Code: 025006

Type of Pesticide: Insect repellent, insect growth regulator (anti-feedant), insecticide.

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

III. REGULATORY BACKGROUND

On August 2, 2007, Plasma Power of India, submitted an application for the registration of the end use product (EP) Plasma Neem™ Oil (azadirachtin 3000 ppm) Insecticide (84185-U), and Plasma Neem™ Oil Manufacturing Use Product (84185-G). Both products contain 100% Cold Pressed Neem Oil. A notice of receipt of the application for registration of Cold Pressed Neem Oil as a new active ingredient was published in the Federal Register on October 24, 2007 (72 FR 60365), with a 30-day comment period. No comments were received following this publication.

Consistent with the Agency's new policy for making pesticide registration actions more transparent, EPA provided a 30-day public comment period on the decision to register Cold Pressed Neem Oil. No comments were received during the 30 day public comment period

On September 19, 2011, Terramera, Inc., submitted an application for the registration of end-use products (EPs) TER-RTU1 (88760-R), containing 5.5% Cold Pressed Neem Oil, and TER-CX1 (88760-E), containing 22.0% Cold Pressed Neem Oil. These EPs indicate a "new use" for this active ingredient (indoor use for the control of bed bugs). A notice of receipt of the application for registration of Cold Pressed Neem Oil for indoor use was published in the Federal Register on November 9, 2011 (76 FR 69730), with a 30-day comment period. No comments were received following this publication.

Consistent with the Agency's policy of making registration actions more transparent, the registration of the TER-RTU1 and TER-CX1 EPs was subject to a 30-day comment period as a "first indoor use" for Cold Pressed Neem Oil. No comments were received following this publication. EPA believes that, based on the information submitted in support of the registration of Cold Pressed Neem Oil for indoor use, it is in the best interest of the public and the environment to issue these registrations. The basis for this decision can be found in the risk assessment for Cold Pressed Neem Oil, which is characterized in this BRAD.

A. Classification

The Biochemical Classification Committee determined that Cold Pressed Neem Oil is a biochemical pesticide due to its apparent non-toxic mode of action and natural occurrence in the environment.

B. Food Clearances/Tolerances

Plasma Power of India filed a petition (PP 7F7249) proposing to establish an exemption from the requirement of a tolerance for residues of Cold Pressed Neem Oil in or on all food commodities. A notice of filing was published on November 2, 2007 (72 FR 62237). On October 13, 2009, EPA promulgated a final rule exempting residues of the biochemical pesticide Cold Pressed Neem Oil, from the requirement for tolerance in or on all food commodities.

IV. RISK ASSESSMENT

A. Active Ingredient Characterization

Cold Pressed Neem Oil is pressed directly from seeds of the Neem tree (*Azadirachta indica*), which is a tropical evergreen tree native to India and also found in other Southeast Asian and African countries. Cold Pressed Neem Oil has a brown color, a bitter taste and a garlic/sulfur smell. A single seed may contain up to 50 percent oil by weight. Cold Pressed Neem Oil contains various compounds that have insecticidal and medicinal properties. It is used in making shampoos, toothpaste, soaps, cosmetics, mosquito repellents, creams and lotions, and pet products such as pet shampoo. It also contains vitamin E, other essential amino acids and fatty acids. Cold Pressed Neem Oil is used for treating many skin diseases, including eczema, psoriasis, and skin allergies.

Cold Pressed Neem Oil is a mixture of several C₂₆ terpenoids that are naturally occurring organic compounds composed of a five-carbon skeleton (simple terpenoids) or complex terpenoids with structures that possess between 20 and 40 carbon atoms. Azadirachtin, the most common terpenoid in Cold Pressed Neem Oil and the most thoroughly characterized, is a federally registered active ingredient pesticide. Cold Pressed Neem Oil also contains steroids, fatty acids, and a number of essential oils.

Descriptions of the technical grade active ingredient (TGAI) product formulation and production process, as well as the formation of impurities, were examined by the Agency and found to meet current standards. A preliminary analysis was conducted to determine Cold Pressed Neem Oil content in five batches of the product, and the results were determined to be acceptable by the Agency. The analytical method used to determine the content of the active ingredient is also acceptable. Physical and chemical properties were submitted for the TGAI 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. All product chemistry data requirements for registration of Cold Pressed Neem Oil have been satisfied.

B. Human Health Assessment

1. Toxicology

Toxicity categories are assigned based on the hazard(s) identified from studies and/or information on file with the Agency. An active ingredient is classified into Toxicity Category I, II, III or IV, in which Toxicity Category I indicates the highest toxicity and Toxicity Category IV indicates the lowest toxicity.

Adequate mammalian toxicology data/information is available to support registration of Cold Pressed Neem Oil. All toxicology data requirements for Cold Pressed Neem Oil 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).

Tier I toxicity data submitted and reviewed showed that Cold Pressed Neem Oil is a toxicity category IV (low toxicity) compound via acute oral and acute inhalation routes of exposure. Cold Pressed Neem Oil is in Toxicity Category III (slightly toxic) for acute dermal irritation. Cold Pressed Neem Oil is not an eye or skin irritant, and it is not a dermal sensitizer. No additional toxicity data are required to support usage of this biochemical.

For more information regarding the acute toxicity data requirements, refer to Table 3 in Appendix A.

b. Sub-chronic 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.

To address the 90-day oral toxicity the data requirement as appropriate for an agricultural registration, the applicant submitted data obtained from the technical public literature in lieu of a guideline study. The study showed that test animals did not exhibit any clinical signs of toxicity that were statistically different from untreated controls. There were no significant changes in body weight, serum liver damage indicators, direct bilirubin and total bilirubin, or other blood parameters during the 90-day study period. The 90-day oral feeding LD₅₀ is higher than 5000 mg crude Cold Pressed Neem Oil/kg body weight. Based on the review of this data, the Agency concluded that no subchronic oral toxicity is expected to occur when this compound is used in accordance with good agricultural practices.

The 90-day dermal and 90-day inhalation toxicity data requirements were waived for the initial agricultural use of Cold Pressed Neem Oil. For the addition of a “first indoor use,” these data requirements have been fulfilled using rationale supported by published scientific literature. Specifically, dermal metabolism of the product is not expected to differ from its oral metabolism (EPA, 2009). In the acute guideline studies, the product was demonstrated to have no acute

dermal toxicity ($LD_{50} > 4000$ mg/kg), was not a dermal irritant, and was not a dermal sensitizer. Similarly, there is a lack of inhalation toxicity (Toxicity Category IV) demonstrated in the submitted acute inhalation toxicity study ($LC_{50} > 2.11$ mg/L). In addition, repeated inhalation exposure is mitigated by indoor use label language requiring a four hour re-entry period after application of the product. Alongside the low toxicity present in the acute and subchronic studies, the Agency concludes that no subchronic dermal or inhalation toxicity is expected to occur when used in accordance with good agricultural practice and when used indoors in accordance with label instructions.

Furthermore, humans are regularly exposed to this substance in medicinal and cosmetic products, via the oral, inhalation and dermal routes, and at comparatively high levels (Schmutterer, 1995). These uses are also expected to result in exposures that are significantly greater than that which would be expected from pesticidal uses, including both agricultural and indoor uses.

For more information regarding the subchronic data requirements, refer to Table 3 in Appendix A.

c. Developmental Toxicity and Mutagenicity

Studies from technical public literature were submitted to address the data requirements for developmental toxicity and mutagenicity (OPPTS 870.3700).

Based on *In vitro* and *in vivo* studies, and subcutaneous and intravaginal applications of Cold Pressed Neem Oil, it seems that developmental toxicity may occur in test animals when exposed to Cold Pressed Neem Oil by intravaginal, intrauterine, subcutaneous injection, or by direct exposure to mammalian sperm and eggs in *in vitro* laboratory studies. The three generation study in rats fed Cold Pressed Neem Oil in the diet, however, demonstrates that chronic oral ingestion of food commodities containing Cold Pressed Neem Oil residues does not result in any mammalian developmental toxicity. Taken together, these data demonstrate that no developmental toxicity is expected to occur from the use of Cold Pressed Neem Oil as a pesticide.

Furthermore, Cold Pressed Neem Oil and its components are not structurally related to known mutagens, nor do they belong to any chemical class of compounds containing known mutagens. Humans are regularly exposed to this substance via oral exposure (as a traditional folk medicinal product) and dermal exposure (when used on skin and hair) at levels that are significantly greater than that which would be expected from the product as a pesticide under conditions of use. In addition, an extensive literature search of several scientific databases (i.e. ChemIDPlus, HSDB, Toxline, CCCRIS, DART, GENETOX, IRIS, ITER, LactMed, Multi-Database, TRI, HazMap, Household Products, TOXMAP and TOXNET) for the period 1980 to 2008 failed to locate any other data / information regarding mutagenicity or genotoxicity of Cold Pressed Neem Oil. As a result, EPA concludes that Cold Pressed Neem Oil is not mutagenic or genotoxic.

d. Effects on the Endocrine System

EPA is required under the Federal Food, Drug, and Cosmetics Act (FFDCA) 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. When the appropriate screening and/or testing protocols being considered under the Agency’s Endocrine Disruptor Screening Program (EDSP) have been developed and vetted, Cold Pressed Neem Oil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

2. Dose Response Assessment

No meaningful toxicological endpoints were identified on Cold Pressed Neem Oil when used as a pesticide; therefore, a dose response assessment was not required.

3. Food Quality Protection Act (FQPA) Consideration

a. Dietary Exposure and Risk Characterization

The most likely human exposure to Cold Pressed Neem Oil will occur via dietary exposure (consumption) to treated fruits, seeds, or leafy vegetables. EPA modeling (using the Terrestrial Exposure model (T-REX; EPA, 2005) of potential residues of Cold Pressed Neem Oil following terrestrial treatments indicated that following 12 consecutive applications of 100% Cold Pressed Neem Oil at 7-day intervals, the maximum dietary residues present would be approximately 881 ppm on broadleaf plant foliage; and approximately 98 ppm on fruits, pods, and seeds. The modeling indicated that residues would decline rapidly between foliar applications (approximately 245-440 ppm on broadleaf foliage; and 27-49 ppm on fruits, pods, and seeds) and following the final application (see Table 4 in appendix A). As stated in section B (a) of this document, Cold Pressed Neem Oil is a toxicity category IV for oral exposure ($LD_{50} = >5000$ mg/kg). The estimated maximum theoretical residues likely to be present on edible commodities are 882 ppm. This residue level is approximately 5-fold less than the highest doses used in acute and subchronic laboratory testing (5000 mg/kg) and approximately 20-fold less than chronic laboratory testing (10% in the diet) at which no mortalities or other signs of clinical toxicity were observed. Therefore, based on a lack of acute, subchronic, or chronic toxicity in laboratory testing, estimated maximum residues that are well below the doses used in laboratory testing, and the rapid degradation of Neem Oil in the environment, it is highly unlikely that there will be any adverse effects to humans resulting from dietary exposure to Neem Oil residue.

Moreover, humans are regularly exposed to this compound via consumption of Cold Pressed Neem Oil medicinal products, and at levels that are significantly greater than what would be expected from pesticide applications. EPA has determined that dietary exposure is not a concern because of the low toxicity of this active ingredient and the history of its use without any reports of adverse effects.

b. Drinking Water Exposure and Risk Characterization

No significant drinking water exposure or residues are expected to result from the pesticidal usage of Cold Pressed Neem Oil. The outdoor use of this active ingredient is intended as a foliar

application on food commodities and not to be applied directly to water. If used in accordance with EPA-approved labeling, is not likely to accumulate in drinking water. In the unlikely event that exposure via drinking water did occur from accidental spraying, the health risk would be expected to be minimal, based on the low acute oral toxicity and the long history of human exposure to Cold Pressed Neem Oil without adverse effects.

As a result, dietary and drinking water exposure to residue of Cold Pressed Neem Oil are expected to be minimal.

c. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

FFDCA section 408 provides that the Agency shall apply an additional tenfold margin of exposure (safety) for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database unless the Agency determines that a different margin of exposure (safety) will be safe for infants and children. Margins of exposure (safety) are often referred to as uncertainty (safety) factors. In this instance, based on all the available information, the Agency has concluded that there is reasonable certainty that no harm to infants and children or adults will result from the use of Cold Pressed Neem Oil when label instructions are followed.

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

a. Occupational Exposure and Risk Characterization

The potential for dermal, eye, and inhalation exposure to Cold Pressed Neem Oil for handlers and applicators is mitigated as long as products are used according to label directions. The Agency will require labels to include the appropriate signal word, re-entry interval and precautionary statements, including the requirement for personal protective equipment, to mitigate any risk of exposure.

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

As stated above, 90-day oral data show very low toxicity, indicating no concern for oral exposure, such as hand-to-mouth, that may occur during indoor residential use. Furthermore, humans are regularly exposed to this substance in medicinal and cosmetic products, via the oral, inhalation and dermal routes, and at comparatively high levels (Schmutterer, 1995). These uses are also expected to result in exposures that are significantly greater than that which would be expected from pesticidal uses, including hand-to-mouth exposure.

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish an exemption from a tolerance, the Agency consider "available information concerning the cumulative effects of [a particular pesticide's] residues and other substances that have a common mechanism of toxicity." These considerations include the possible cumulative effects of such residues on infants and children.

5. Cumulative Effects

EPA has considered the potential for cumulative effects of Cold Pressed Neem Oil and other substances in relation to a common mechanism of toxicity. However, because of its low toxicity to mammalian systems, the Agency does not expect any cumulative or incremental effects from exposure to residues of Cold Pressed Neem Oil when applied/used as directed on the label and in accordance with good agricultural practices.

6. Risk Characterization

The Agency considered human exposure to Cold Pressed Neem Oil 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 Cold Pressed Neem Oil when label instructions are followed.

C. Environmental Assessment

1. Ecological Hazards

Adequate non-target toxicology data/information are available to support registration of Cold Pressed Neem Oil. All non-target toxicology data requirements for Cold Pressed Neem Oil have been satisfied.

There are no concerns for any non-target organisms when 100% Cold Pressed Neem oil is applied in accordance with EPA-approved label use directions. No toxic endpoints have been identified for non-target birds, non-target plants, and non-target soil organism such as earthworms. Although Cold Pressed Neem Oil is slightly toxic to aquatic organisms in laboratory testing, as a result of the rapid biodegradation of Neem Oil under approved conditions of use, calculated Risk Quotients (RQs) for fish and aquatic invertebrates are well below any Levels of Concern (LOCs) for threatened and endangered species. There are no concerns for non-target insects. Only insects that feed directly on treated plant foliage or roots will be directly exposed to Cold Pressed Neem Oil at levels that will be pesticidal. Honey bees and other pollinators that feed on nectar, and predators of insect pests are unlikely to consume sufficient quantities of Cold Pressed Neem Oil to cause adverse effects. Bees have been reported to avoid foods that contain >100 ppm Cold Pressed Neem Oil.

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

2. Environmental Fate and Ground Water Data

Since Cold Pressed Neem Oil is a multicomponent mixture, azadirachtin A was used as a surrogate when evaluating environmental fate for all of the insecticidally active liminoid components in 100% Cold Pressed Neem Oil.

A number of studies have addressed the degradation of Cold Pressed Neem Oil components in the environment. In forest environments, azadirachtin A persisted 3 to 6 days in terrestrial matrices and 8 to 13 days in water (Sundaram et al., 1999). In laboratory studies, azadirachtin A

was shown to have temperature dependent degradation rates in sandy loam soils with half-lives of 43.9 and 19.8 days at 15 °C and 25 °C, respectively (Stark and Walter, 1995). When the soil was autoclaved, half-lives increased to 91.2 (15 °C) and 31.5 days (25 °C), demonstrating the significant influence of microbial activity in the degradation of Cold Pressed Neem Oil. Half lives for azadirachtin B in sandy loam soil were comparable to that of azadirachtin A. Azadirachtin is extremely labile in light with photolysis half lives of 48 min to 3.98 days in thin films under UV light, and 2.47 days on leaf surfaces (Johnson et al., 2003). In field trials with olives, azadirachtin residues had a half-life of 0.8 days (Caboni et al., 2002).

Based on the submitted data, Cold Pressed Neem Oil is readily biodegradable in soil, water and on foliar surfaces. As a result, Cold Pressed Neem Oil and its components are not likely to persist in the environment.

3. Ecological Exposure and Risk Characterization

The potential for exposure to non-target wildlife is minimal. Based on the results/information presented in the Environmental Fate and Groundwater Data section above, it is highly unlikely that non-target organisms, particularly aquatic organisms, would be exposed to potentially toxic levels of Cold Pressed Neem Oil via runoff and/or movement through the soil. Cold Pressed Neem Oil undergoes rapid biodegradation in soil and water, and no unreasonable adverse effects to the environment are expected from the use of Cold Pressed Neem Oil when label instructions are followed.

4. Endangered Species Assessment

A nontarget organism hazard assessment and an Endangered Species Assessment has been conducted to support registration of Plasma Neem Oil Manufacturing Use Product and Plasma Neem Oil Biological Insecticide (an end-use product, EP) (the MP and the EP are identical formulations). There are no concerns for non-target mammals and birds, including threatened and endangered species. No toxic endpoints were identified for non-target terrestrial mammals (acute oral and dietary toxicity LD₅₀s >5000 mg/kg and 5000 ppm, respectively) and birds (acute oral and dietary toxicity LD₅₀s >1000 mg/kg and 12000 ppm, respectively). Moreover, based on submitted laboratory studies, no concerns were identified for non-target aquatic organisms, including threatened and endangered species. Calculated Risk Quotients (RQs) fish and aquatic invertebrates are well below any Levels of Concerns (LOCs) for threatened and endangered species.

Based on the fact that Cold Pressed Neem Oil is not toxic to non-target organisms and on its use pattern and use instructions, EPA has determined it will have "No Effect" on any currently listed threatened or endangered species or any designated critical habitat.

D. Product Performance (Efficacy)

Customarily, the Agency requires product performance (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, collectively referred to as "public health pests." 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).

In accordance with Agency policy regarding “public health pests,” Terramera, Inc., has submitted efficacy data in support of the registration of the TER-RTU1 and TER-CX1 EPs for indoor use to control bed bugs. Trials conducted at product label rates showed control of bed bug adults, nymphs and eggs. Treatment residues on various substrates (painted and unpainted wood, carpet, mattress swatches and filter paper) killed all adults in less than 24 hours, and direct spray killed all adults in less than 8 hours. Bed bug eggs exposed to dried residues, wet residues and direct sprays of treatment all did not hatch. Treatment on wood substrate remained active in preventing nearly all egg hatch for up to 19 days post treatment. Retreatment interval for control of adults and nymphs was found to be 14 days (up to 100% for 10 days and 90% or greater for 14 days on wood), and for control of eggs was found to be 21 days (up to 100% for 18 days and 80% or greater for up to 21 days).

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 Cold Pressed Neem Oil. 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, Cold Pressed Neem Oil is eligible for registration for the labeled uses.

B. Regulatory Decision

EPA has determined that Cold Pressed Neem Oil, in either agricultural or indoor use practices, presents no issues of toxicological, ecological, or environmental concern. As discussed above, acute toxicity data for Cold Pressed Neem Oil demonstrate that it is either toxicity category IV or III. Cold Pressed Neem Oil does not demonstrate subchronic or developmental toxicity, and it is not mutagenic or genotoxic. EPA has no concerns for any non-target organisms exposed to Cold Pressed Neem Oil in accordance with approved label directions. EPA has not identified any toxic endpoints for non-target mammals, birds, plants, aquatic, or soil organisms. Nor are there concerns for any threatened and endangered species. Thus, given that Cold Pressed Neem Oil has very low toxicity and presents little if any risk to non-target organisms, EPA concludes that it is in the best interests of the public and the environment to both issue the registration for Cold Pressed Neem Oil and to approve its use indoors. Consistent with the Agency’s policy for making these registration actions more transparent, EPA has provided one 30-day public comment period on the decision to register Cold Pressed Neem Oil and an additional 30-day public comment period on the decision to approve the “first indoor use” of Cold Pressed Neem

Oil. No comments were received during either comment period.

The data submitted fulfill the requirements of registration of Cold Pressed Neem Oil for use in on all outdoor and greenhouse ornamental and food crops to control insects using ground equipment, and indoors for the control of bed bugs. Refer to Appendix B for product-specific information.

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 Cold pressed Neem Oil, 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 Cold Pressed Neem Oil 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.

Notwithstanding 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

TABLE 1. Product Chemistry Data Requirements for Cold Pressed Neem Oil (40 CFR § 158.2030)		
Biochemical Data Requirement by OCSPP Guideline Number	MRID(s)	Description of Result
880.1100 Product identity; 880.1200 Manufacturing process; 880.1400 Discussion of formation of unintentional ingredients	47538701	Submitted data satisfy the requirements for product identity, manufacturing process, and discussion of formation of impurities.
830.1700 Analysis of samples	47538701	Submitted data satisfy the requirements for analysis of samples.
830.1750 Certified limits	47538701	Not required for TGAIs.
830.1800 Enforcement analytical method	47538701	Not required for TGAIs.

TABLE 2. Physical and Chemical Properties of Cold Pressed Neem Oil (40 CFR § 158.2030)		
Biochemical Data Requirement by OCSPP Guideline Number	MRID(s)	Description of Result
830.6302 Color	^a	Yellowish brown
830.6303 Physical State	^a	Liquid at 20°C
830.6304 Odor	^a	Strong, garlic-like
830.6313 Stability	47476701	10% degradation at 11 months under unregulated storage conditions/shipment
830.7000 pH	^a	5.3 at 21°C (70°F)
830.7050 UV/Visible Absorption	^a	215 nm
830.7200 Melting Range	^a	Not applicable; product is a liquid
830.7220 Boiling Range	^a	BP > 200°C (392°F)
830.7300 Density/Relative Density/Bulk Density	^a	0.922 g/mL (8.27 lb/gal) at 22°C (72°F)
830.7370 Dissociation Constant in Water	^a	Not applicable; the product does not substantially dissociate in water
830.7550 Partition Coefficient	^a	Log K _{ow} = 6.26
830.7840 Water Solubility	^a	52.3 mg/L
830.7950 Vapor Pressure	^a	2.5 x 10 ⁻⁷ mm Hg at 25°C

^a Data submitted via self certification per Pesticide Registration Notice (PRN) 98-1.

Table 3. Human Toxicology Data Requirements for Cold Pressed Neem Oil (40 CFR § 158.2050)			
Biochemical Data Requirement by OCSPP Guideline Number	MRID(s)	Description of Result	Toxicity Category
870.1100 Acute oral [rat] toxicity	47088002 ¹ 47208801 ²	LD ₅₀ = >5000 mg/kg for female	IV
870.1200 Acute dermal [rabbits] toxicity	47088003 ¹ 47208802 ²	LD ₅₀ = >2000 mg/kg for males, females, and combined	III
870.1300 Acute inhalation [rat] toxicity	47088005 ¹ 47208803 ²	The inhalation LC ₅₀ for males, females, and combined was > 2.53 mg/L & > 2.11 mg/L, respectively, at concentrations of azadirachtin of 0.30% & 0.15%	IV
870.2400 Acute eye irritation [rabbit]	47088006 ¹ 47208804 ²	No irritation was noted on any rabbit throughout the study. Plasma Neem™ Oil was non-irritating.	IV
870.2500 Acute dermal irritation [rabbit]	47088007 ¹	No irritation was noted on any rabbits throughout the study. The primary irritation index was 0.0. Plasma Neem™ Oil was non-irritating.	IV
870.2600 Skin sensitization [guinea pig]	47088004 ¹	After three consecutive weekly inductions, the test and control animals showed no signs of reactivity at 24 and 48 hours after challenge.	Not a dermal sensitizer
870.3100 90-Day Oral feeding [mouse]	Awad (2003)	LD ₅₀ = >5000 mg/kg	No subchronic oral toxicity
870.3250 90-Day Dermal	47195705 48606014 48751001	The product is not intended for purposeful application to human skin. Neem oil is not known nor expected to be metabolized differently by the dermal route of exposure than by the oral route of exposure. No literature reports of subchronic dermal toxicity.	No subchronic dermal toxicity
870.5100 90-Day Inhalation	47195705 48606014 48751001	The use patterns will not result in significant levels of repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol. Indoor use label language includes 4hr re-entry interval following application. No literature reports of subchronic inhalation toxicity.	No subchronic inhalation toxicity
870.3500 Developmental Toxicity [Teratogenicity]	47195706 (see refs within this MRID)	No reproductive/developmental effects in a 3-gen rat study with 10% Neem Oil in diet. Reproductive/developmental effects occur only in in vitro studies on sperm or eggs, subcutaneous exposure; contraceptive effects with intrauterine/intravaginal exposure	Not a developmental toxicant when used in accordance with approved labeling.
870.5100 Mutagenicity Testing [Ames Assay]	47088008 & Polasa & Rukmini (1987)	No evidence of mutagenicity with or without S-9 activation in <i>S. typhimurim</i>	Not a mutagen

¹ The test material contains 0.30% azadirachtin.

² The test material contains 0.15% azadirachtin.

Table 4: Estimated Cold Pressed Neem Oil residues on terrestrial matrices using the Terrestrial Exposure model (T-Rex; EPA, 2005)			
Terrestrial matrix	Dietary-based Estimated Environmental Concentrations (ppm)		
	0 days after last app	86 days after last app	106 days after last app
Edible broadleaf plant foliage	881.20	0.04	0.00
Fruits, pods, and seeds	97.91	0.00	0.00

TABLE 5. Non-Target Organism Toxicity Requirements for Cold Pressed Neem Oil (40 CFR § 158.2060)				
TABLE 1 Tier I Non-Target Organism Profile				
Guideline No.	Study Type	References and/or MRID(s)	Results	Toxicity Category
870.1100	Acute oral (rat) toxicity	47088002 ¹ 47208801 ²	LD ₅₀ = >5000 mg/kg for female	IV
870.3100	90-Day Oral Feeding (mouse)	Awad (2003) (476335-01)	LD ₅₀ = >5000 mg/kg	No subchronic oral toxicity
850.2100	Avian Acute Oral Toxicity (redwinged-blackbird)	Schafer & Jacobsen. (1983); (47633502)	LD ₅₀ >1000 mg/kg (highest acute dose tested)	No effects at highest dose tested
850.2100	Avian Dietary Toxicity (redwinged-blackbird)	Schafer & Jacobsen. (1983); (47633502)	LD ₅₀ > 10000 ppm (1.0%)	Practically non-toxic
	Avian Dietary Toxicity (Leghorn hen)	Verma et al. (1998) (474787-05)	12-week LD ₅₀ > 12000 ppm (6.0% neem oil in neem cake feed)	Practically non-toxic
850.1075	Fish Toxicity	Awad (2003) (476335-01)	96-hr LC _{50S} = 70.6 – 84.3 ppm	Slightly Toxic
850.1300	Aquatic Invertebrates	Awad (2003) (476335-01)	48-hr LC _{50S} = 57.5 - 63.9 ppm	Slightly Toxic
850.4150	Non-target Plants (vegetative vigor)	476335-04 & -05	No toxicity observed in plants treated with up to 11000 ppm (1.1%) Neem Oil ³	Practically non-toxic
850.3020	Honey bees	Melathoupoulos et al. (2000)	Contact LD ₅₀ > 45 ug/bee (adult)	Practically non-toxic
		Canadian Honey Council (2005)		-

¹ The test material contains 0.30% azadirachtin.

² The test material contains 0.15% azadirachtin.

VIII. Appendix B

For product specific information, please refer to: <http://oaspub.epa.gov/pestlabl/ppls.home>

IX. Appendix C

REFERENCES

Abudulai, M., B. Merle Shepard, and Paula Levin Mitchell. 2004. Effects of neem (*Azadirachta indica* A. Juss.) on predators of *Nezara viridula* (L.) (Hemiptera: Heteroptera: Pentatomidae). *Journal of Agricultural Urban Entomology*. 21(1): 9–13.

Canadian Honey Council (CHC). 2005. Essential oils and their toxicity to honeybees. November-December. <http://www.honeycouncil.ca/users/folder.asp?FolderID=5220>

Da Silva, F. A. C. and S. S. Maritnez. 2004. Effect of neem seed oil aqueous solutions on survival and development of the predator *Cycloneda sanguinea* (L.) (Coleoptera: Coccinellidae).

Extension Toxicology Network (EXTOXNET). 1995. Pesticide Information Profile: Azadirachtin. Cornell University Cooperative Extension. <http://pmp.cce.cornell.edu/profiles/extoxnet/24d-captan/azadirachtin-ext.html>

Food and Agriculture Organization of the United Nations (FAO). 2003. Azadirachtin. FAO Specifications and Evaluations for Agricultural Pesticides. <http://www.fao.org/ag/agpp/pesticid/>

Lowery, D. T. and M. B. Isman. 1995. Toxicity of neem to natural enemies of aphids. *Phytoparasitica* 23(4): 297-306.

Methathopoulos, A. P., M. L. Winston, R. Whittington, T. Smith, C. Lindberg, A. Mukai, M. Moore. 2000. Comparative laboratory toxicity of neem pesticides to honey bees (Hymenoptera: Apidae), their mite parasites *Varroa jacobsoni* (Acari: Varroidae) and *Acarapis woodi* (Acari: Tarsonemidae), and brood pathogens *Paenibacillus larvae* and *Ascospaera apis*. *Entomological Society of America* 93(2):199-209.

Mordue, J. A. and A. Blackwell. 1993. Azadirachtin: An update. *Journal of Insect Physiology* 39: 903-924.

National Research Council. 1992. *Neem: A tree for solving global problems*. National Academy Press, Washington, DC.

Naumann, K. and M. B. Isman. 1996. Toxicity of a neem (*Azadirachta indica* A. Juss) insecticide to larval honeybees. *American Bee Journal*. 7: 518-520.

Rembold, H., G. K. Sharma, C. Czoppelt, and H. Schmutterer. Evidence of growth disruption in insects without feeding inhibition by neem *azadirachta-indica* seed fraction. *Journal of Plant Diseases and Protection* 87:290-297.

Schmutterer, H. 1995. Chapter 6: Medicinal Uses in Asia. *The Neem Tree and Other Meliaceous Plants*. New York: VCH Publishers, 1995. p. 518-525.

Stark, J. D. and J. F. Walter. 1995. Persistence of azadirachtin A and B in soil: Effects of temperature and microbial activity. *Journal of Environmental Science and Health: Part B. Pesticides, food contaminants, and agricultural wastes*. 30: 685-698.

Sundaram, K. M. S., A. Sundarum, J. Curry, and L. Sloane. 1999. Formulation selection, and investigation of azadirachtin-A persistence in some terrestrial and aquatic components of a forest environment. *Pest Management Science* 51(1):74-90.

EPA. 2001. Generic Environmental Estimated Concentration (GENEEC) Version 2.0. Tier One Screening Model for Pesticide Aquatic Ecological Exposure Assessment. Environmental Fate and Effects Division/Office of Pesticide Programs. August 1, 2001.

EPA. 2005. T-REX, Version 1.2.3. Terrestrial Biology and Exposure Teams, Environmental Fate and Effects Division/Office of Pesticide Programs. August 8, 2005.

EPA. 2009. Memo from R. Jones to D. Benmhend. Tolerance Exemption Petition Review Plasma Neem Oil Manufacturing Use Product and Plasma Neem Oil Biological Insecticide. Each Product is Identical and Contains 100% Neem Oil (w/0.3% Azadirachtin) As Its Active Ingredient. March 9, 2009.