MEMORANDUM

SUBJECT: Review of Mammalian Toxicology of the End-Use Product, Nexa Cedarwood Oil Moth Protection, containing the active ingredient, Cedar Oil. (PC Code 040505; File Jacket # 069129-R; Submission: S534429; DP Barcode: D241915)

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I. INTRODUCTION

The Biopesticides and Pollution Prevention Division (BPPD) has reviewed toxicology data and waivers submitted by BioLogic, Inc. to assess potential hazards and exposures to humans and the environment that might result from the proposed use of Nexa Cedarwood Oil Moth Protection, containing the active ingredient, Cedar Oil as an indoor clothes moth repellant.

II. HAZARD IDENTIFICATION

A. Data Waivers

The following waivers were requested by the registrant:

152 Series Toxicology, based on the active ingredient's GRAS status (21 CFR § 172.515) as a synthetic flavoring agent in food by the U. S. Food and Drug Administration, and the Agency's waiver of all toxicology data requirements in the September, 1993 Reregistration Eligibility Decision document.

154 Series Nontarget Organisms, based on the proposed indoor use, there is no exposure to

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birds, fish, plants and aquatic species. Effects to nontarget insects are expected to be negligible. All ecological effects and environmental fate data were also waived in the September, 1993 Reregistration Eligibility document.

All of the waivers requested were considered appropriate by BPPD, based on the above rationale. In addition, cedarwood oil is exempt from regulation under FIFRA § 25(b)(2), at 40 CFR 152.25(g). Although the active ingredient is exempt from regulation under FIFRA, the product contained inerts that were not listed on the List 4A inerts, thus the product must be registered with the Agency. Product chemistry data have been submitted for the product and is the subject of a separate memorandum.

B. Toxicology Data

Although waivers for toxicology were requested and considered appropriate by BPPD, the registrant submitted 4 toxicology studies for review. The summaries follow:

Acute Oral Toxicity (MRID No. 444120-01): CEL 590 16 I VP, containing the active ingredient, cedar wood oil, was administered undiluted to 10 Sprague-Dawley rats (5 per sex) via oral gavage at a single dose (2000 mg/kg), and the animals were observed for lethality and toxic signs for 14 days. The only toxic signs noted was slight to moderate "apathy" for approximately 30 minutes post-exposure, which presumably means lethargy or inactivity. No deaths occurred during the study. No gross lesions were observed in any organs at necropsy. The study is **acceptable**, and the **LD50 is > 2000 mg/kg**. This places the test material in acute oral **Toxicity Category III**.

Pilot Study Inhalation Toxicity (MRID No. 444120-02): CEL 590 16 I VP, containing the active ingredient, cedar wood oil, was administered to 10 Sprague-Dawley rats (5 per sex) via the inhalation route for 28 days. This was accomplished by placing the rats in containers that were covered up to 90% in plastic, and a plastic blister pack with a dispenser volume of 9 ml test substance was fastened onto the cage. The main ingredients in CEL 590 16 I VP, (-)-α-cedrene and (+)-cedrol, were analyzed by gas chromatography of air samples and adsorption onto charcoal filters on days 1-3, 25 and 28. This demonstrated that the exposure to (-)-α-cedrene decreased from 484 mg/m^3 on day 1, to 137 mg/m^3 on day 28, while the concentration of (+)-cedrol remained more constant at 67 mg/m^3 on day 1 and 47 mg/m^3 on day 28. The rats tried to avoid the smell of the test substance by burrowing into the cage bedding, and tried to stay as far away from the source as possible. No toxic signs nor deaths occurred during the study. Two animals per sex were sacrificed and necropsied at the end of the study, and no gross lesions were observed. The study is not acceptable (nor upgradeable) for an acute or subchronic (90-day) inhalation study, according to EPA guidelines (§ 81-3/152-12 or 82-4). In order to qualify as an acceptable study under EPA guidelines, an inhalation study must be performed with a dynamic air flow through in an inhalation chamber, equipped to measure oxygen concentration and test substance concentration in the breathing zone, and air particle size analysis. All of these measurements must be performed in order to determine the actual dose/respirable particle sizes

experienced by the animals during treatment. Although samplings of air and charcoal filters were performed, the information is limited to the first 3 days and days 25 and 28 of the study. No measurements were performed during the rest of the study. It is obvious that the material was dissipating during the course of the study, and thus the animals were clearly not dosed at a constant rate.

Acute Eye Irritation (MRID No. 444120-03): CEL 590 16 I VP, containing the active ingredient, cedar wood oil, was administered undiluted into the right eyes of 3 albino rabbits (2 females, 1 male) in a single dose (0.1 ml). After 24 hours, the eyes were rinsed and the animals were observed for eye irritation for 6 days. All three animals developed slight conjunctival redness (hyperemia) at a grade 1 (out of a maximum of 3) level, but this disappeared after the first day of testing in the females, and by day 2 in the male. No other signs of irritation were noted. No acute toxic signs or deaths occurred during the study. The study is **acceptable**, and places the test material in acute oral **Toxicity Category III for eye irritation**.

Skin Sensitization Study According to Magnusson & Kligman (MRID No. 444120-04): CEL 590 16 I VP, containing the active ingredient, cedar wood oil, was tested for dermal sensitization in Pirbright White Strain guinea pigs (5/sex) using the method of Magnusson and Kligman. Two studies were performed, the first was to determine the validity of the study in the Pirbright White Strain of guinea pigs using a known dermal sensitizer, p-phenylenediamine, and the second evaluated the test substance. Ten test animals (5/sex) and 5 controls (3 females, 2 males) were used in both studies.

After two induction doses (one intradermally injected with complete Freund's adjuvant, and one dermally applied on a gauze patch six days later), the animals were challenged on day 21 of the study. The animals sensitized with p-phenylenediamine responded appropriately to this moderate sensitizer, while the animals exposed to CEL 590 16 I VP did not exhibit an allergic response following the challenge dose. No deaths or signs of clinical toxicity occurred. The study is **acceptable**. The test substance is **not a dermal sensitizer** when tested by the method of Magnusson & Kligman

III. DIETARY RISK CHARACTERIZATION

No dietary risk is expected due to the non-food use of this product.

IV. OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

No dermal, oral or inhalation exposure estimate were submitted. The primary use of this product is for use in the home setting, i.e., clothes closets, thus, no occupational exposure is expected. In addition, it is formulated into a dispenser, and thus very little exposure is expected if used according to label directions.

V. AGGREGATE EXPOSURE

There are no existing tolerances or tolerance exemptions for cedarwood oil. No maximum residue limits have been established for cedarwood oil by the Codex Alimentarius commission, and there is no Maximum Contaminant Level for residues in drinking water under the Safe Drinking Water Act. Cedarwood oil is generally recognized as safe (GRAS) for use as a flavoring agent in foods. Based on these considerations, and the lack of exposure described in the hazard assessment above, an assessment of aggregate exposure as not been conducted for cedarwood oil.

VI. OTHER FOOD QUALITY PROTECTION ACT CONSIDERATIONS

A. Cumulative risk from exposure to substances with a common mechanism of toxicity. Section 408(b)(2)(D)(v) of the Food Quality Protection Act (FQPA) requires that when considering whether to establish, modify, or revoke 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." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have methodologies to resolve the complex scientific issues concerning common mechanisms of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question, such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions of specific classes of pesticide chemicals will be heavily dependent upon specific data, much of which may not be presently available.

The subject end-use product, containing cedarwood oil as the active ingredient, is intended only for a non-food, indoor use as an insect repellant. Its activity is non-toxic to the target pest, clothing moths. The U.S. Food and Drug Administration and the Flavor and Extract Manufacturer's Association has designated cedarwood oil as GRAS for use as a synthetic flavoring agent in food. Cedarwood is found in mulch bedding materials, linings of closets and storage chests for clothing, and cedarwood oil is used as fragrance in a variety of home-use products. Such widespread use and its non-toxic mode of activity when used as an insect repellant precludes attempting a cumulative risk assessment for this biochemical pesticide and related substances.

B. Endocrine disrupter effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect... ." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of the FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of cedarwood oil for endocrine effects.

C. Determination of Safety (U.S. Population, infants and children)

Exposure to this pesticidal product is considered to be minimal to non-existent, since it is contained within a dispenser and its use in clothes closets or other enclosed spaces as a clothing moth repellant. This product has been classified in Toxicity Category III for acute oral toxicity, and has been generally recognized as safe by the U.S. FDA and FEMA as a synthetic food flavoring ingredient. Therefore, there is reasonable certainty of no harm to the U.S. populations or sensitive subpopulations, including infants and children, based on the use of cedarwood oil as the active ingredient in a moth repellant.

D. Environmental Assessment

The use of cedarwood oil as an indoor moth repellant and its exemption from regulation under FIFRA 25(b)(2) have been considered appropriate for waiver of conditionally required ecological toxicity studies (Avian Acute Oral 154-6; Avian Dietary 154-7; Freshwater Fish LC50 154-8; and Freshwater Invertebrate LC50 154-9).

No significant exposure of non-target organisms, both wildlife and aquatic, is likely as a direct result of this end-use product, as long as the product is used and disposed of according to its label directions.

VII. CONCLUSIONS

Based upon the evaluation of the submitted information, there is reasonable certainty of no harm to humans or the environment from the use of Nexa Cedarwood Oil Moth Protection. The label should bear appropriate precautionary labeling for Toxicity category III oral and eye irritation. No acute dermal toxicity, irritation or inhalation studies were submitted and were waived; although no inhalation exposure is expected, it may be considered appropriate to label the product according to Toxicity Category III for dermal toxicity and/or irritation, in the event a package is accidentally opened and the contents are in contact with the skin.