Registration Decision
for
Nootkatone

A New Active Ingredient
(4R,4aS,6R)-4,4a-Dimethyl-6-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one

PC Code: 030806

Approved by:

for

Ed Messina, Esq., Acting Director
Office of Pesticide Programs
U.S. Environmental Protection Agency

Date:

August 7, 2020

Table of Contents

1. Introduction

This document announces that the Environmental Protection Agency (EPA) has completed its initial evaluation of the new biochemical active ingredient (4R,4aS,6R)-4, 4a-dimethyl-6-(prop-1 -en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, herein referred to as nootkatone. The application submitted to EPA was for a manufacturing-use product only, without an accompanying end-use product registration. In the absence of a label for an end-use product, EPA evaluated four use scenarios based on input from the applicant about potential end-use products and their uses, compositions, applications rates and methods. Based on those assumptions for use, this document discusses the two uses that EPA has concluded meet the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) standard for registration[1]. EPA sought public comments on its proposed decision. Two comments were received.

The Centers for Disease Control and Prevention (CDC) led the research and development of nootkatone to be formulated into end-use pesticide products aimed at protecting people and pets. In 2017, CDC partnered with the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, to award a contract with the key objectives of advancing the development of nootkatone and eventually, nootkatone-based products for protection against mosquito-borne diseases.

Nootkatone is a naturally occurring sesquiterpene ketone and a volatile essential oil most notably found in grapefruit and in the Alaska Yellow Cedar (*Chamaecyparis nootkatensis*), a species of tree. Its odor and flavor are typical of grapefruit and grapefruit peel oil. In its solid form it is usually found as colorless crystals. Humans are regularly exposed to nootkatone from the consumption of grapefruit juice, and to a lesser extent, orange juice and other foods and beverages containing this compound. Moreover, humans are exposed to nootkatone through its use in fragrances and cosmetics.

Nootkatone is currently approved by the Food and Drug Administration (FDA) as a synthetic flavoring substance and adjuvant for direct addition to food (21 CFR 172.515). It is also used as a fragrance. No safety concerns were identified at estimated levels of exposure (dietary) in the United States (0.3 µg/kg bw/day) when the chemical was evaluated in 2004 by the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) (WHO, 2004).

As a pesticide, nootkatone is being registered as an active ingredient in a technical/manufacturing-use product (MP). As noted above, in evaluating a new active ingredient for registration and in order to make a FIFRA finding, EPA typically looks to the end-use product registrations containing that new active ingredient to assess likely exposures and risks from use of the pesticide. The end-use product registrations that generally accompany the

[1] While EPA evaluated four theoretical use scenarios, only two of those scenarios have been determined to meet the FIFRA standard for registration and for that reason, are discussed in this decision document. The two other scenarios that did not meet the FIFRA standard have been withdrawn by the applicant from further consideration. However, a discussion and information regarding EPA's risk assessment relative to all four of the theoretical scenarios can be found in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0122" at www.regulations.gov).

technical/MP application for registration contain data and information necessary for EPA to assess the likely exposure expected from use of the product and when compared with the toxicity of the product, to be able to assess potential risks from use of that product. For pesticides such as insect repellents or other pesticides that will have public health claims, efficacy data specific to the end-use product registration is required to be submitted so that EPA can evaluate that data to ensure that such claims are supported due to the potential harm if the products do not work as intended. In addition, end-use product (EP) composition (e.g., percentage of active ingredient, identity of inert ingredients) and specific labeling information that describes the manner in which the product is to be used by the ultimate end-user (based on data), accompanies the EP registration application. EPA uses this information to evaluate exposure to humans and the environment, calculate risks to users, workers, and the environment, and make its determination about whether the pesticide, when used as intended, will cause unreasonable adverse effects on the environment. Without an accompanying end-use product, it is difficult to know exactly how users, workers, or the environment will be exposed to the pesticide and if risks are likely to be outweighed by benefits when the theoretical end-use product is used as intended.

This is why, in the case of this technical/MP application, EPA requested additional information about the end-use products that might be formulated from this technical/MP product. As stated above, the applicant identified theoretical use scenarios for future nonfood, end-use product registrations for EPA evaluation. EPA is registering this MP product for the scenarios that EPA has determined meet the FIFRA standard for registration, which would allow the MP to be formulated into end-use products, with the following restrictions, pending further evaluation after the receipt of additional data described below:

1. Dermally applied skin repellent can contain no more than 20% active ingredient; Maximum application rate cannot exceed 0.4mg/cm^2 skin/day; Application frequency cannot be applied more than 4x/day.

2. Low volume or ultra-low volume spray (terrestrial nonfood) for mosquito control may be applied in the following manner: vehicle-mounted ground spray and fixed-wing rotary aerial spray at no more than 60% active ingredient. Maximum application rates up to 3 oz/acre at 60% nootkatone equivalent to up to 55g (0.12 lbs active ingredient/acre); Application frequency may be on an as needed, targeted basis. Any residues in or on food from use of this product must be covered by a tolerance or exemption. A petition to establish such a tolerance or exemption must be submitted and approved by EPA under section 408 of the FFDCA, or EPA must confirm that an existing tolerance or exemption already covers such residues.

However, such EP products also need to go through an EPA review to determine that they meet the FIFRA standard of registration. EPA will require such applications to include all data that EPA determines is necessary to support that registration, including, but not necessarily limited to, efficacy data, dermal absorption data, and enzyme inhibition/metabolism data to evaluate potential interactions with various drugs.

In the absence of actual end-use product registrations, EPA has therefore conducted an assessment using the given parameters provided by the applicant to: (1) assess the potential risks associated with potential EP use patterns; and (2) inform the most appropriate labeling language

for the MP. A detailed discussion relating to risks and labeling language can be found in section 3.1.3 and section 7 of this document.

In terms of its human health toxicity, nootkatone is of low acute toxicity for all routes of exposure. No dietary toxicological endpoints of concern were identified, although toxicological endpoints were identified for subchronic dermal and inhalation toxicity. A summary of EPA's findings from this assessment for the uses that EPA is registering can be found in section 3.1.3 of this document.

EPA also considered nootkatone's potential effects on nontarget organisms (birds, mammals, insects, plants & aquatic organisms). Nootkatone is classified as practically non-toxic to birds, mammals, and bees. Adverse effects to these taxa are not anticipated from the use scenarios being proposed. Nootkatone is not expected to pose a risk to aquatic organisms at any of the proposed application rates or methods. As a result of the overall low toxicity profile and limited exposure anticipated from the specified scenarios, EPA is able to the make a "no effect" determination for direct and indirect effects to federally listed threatened and endangered ("listed") species and their designated critical habitats.

After reviewing all submitted information and based on this exploratory assessment, EPA has concluded that the manufacturing-use product may be registered for formulation only into end-use products that meet a number of conditions. As previously noted, end-use products formulated with nootkatone cannot be sold or distributed without first being evaluated and registered by EPA. Conditions for end-use products include: additional data, including efficacy data which concludes that use of those products will not cause unreasonable adverse effects to human health or the environment; end-use products may only be used as a dermally-applied insect repellent or a low-volume or ultra-low-volume area-wide mosquitocide spray; the end-use product must meet product formulation requirements and contain prescribed restrictions on directions for use as described in section 7 of this document; the end-use product must not result in residues in or on food, unless a tolerance or exemption from the requirement of tolerance for such residues is established or confirmed; and finally, data must be provided to enable the Agency to assess the potential risk from interaction with prescription and over-the-counter drugs, including dermal absorption data for the end-use product formulation and *in vitro* metabolism data on potential drug interactions. EPA will accept *in vitro* dermal absorption data in human tissues tested according to OECD Guideline 428 (https://www.oecd-ilibrary.org/environment/test-no-428-skin-absorption-in-vitro-method_9789264071087-en). EPA recommends using guidance from FDA's Center for Drug Evaluation and Research entitled "In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, Guidance for Industry" (Section III , Evaluating Metabolism-Mediated Drug Interactions; https://www.fda.gov/media/134581/download).

Therefore, the Agency is granting the unconditional registration of the new active ingredient, nootkatone (EPA File Symbol 91873-R), for the two specified uses under FIFRA section 3(c)(5).

2. Background

Nootkatone was first classified as a biochemical pesticide by EPA's Biochemical Classification Committee (BCC) on August 17, 2015, because it was understood to meet the three criteria for

biochemical classification: (i) is a naturally-occurring substance or structurally-similar and functionally identical to a naturally-occurring substance; (ii) has a history of exposure to humans and the environment demonstrating minimal toxicity, or in the case of a synthetically-derived biochemical pesticide, is equivalent to a naturally-occurring substance that has such a history; and (iii) has a non-toxic mode of action to the target pest(s). The anticipated uses for nootkatone at that time consisted of use as an insect repellent.

On December 13, 2017, the U.S. Environmental Protection Agency ("EPA") received an application from Sci Reg, Inc. (on behalf of Evolva) for the registration of a technical/MP pesticide product containing the new biochemical active ingredient nootkatone. Sci Reg, Inc. provided a battery of acute studies; subchronic oral, dermal and inhalation toxicity studies; a prenatal developmental toxicity study; and two genotoxicity studies. In the Federal Register of October 15, 2018 (83 FR 51942), EPA published a Notice of Receipt (NOR) that announced receipt of a new product application containing the new active ingredient, nootkatone.

In December 2018, nootkatone's classification was reevaluated to better understand the chemical's mode of action as there was also a potential that nootkatone could be used as an insecticide. On March 11, 2019, EPA classified nootkatone as a "biochemical-like" substance, based on the Weight-of-Evidence (WOE), even though it does not meet Criterion (iii) for classification as having a non-toxic mode of action to the target pest as the MOA remains uncertain. A review of new data and information could prompt the EPA to re-evaluate the classification for nootkatone**.**

3. Evaluation

In evaluating a pesticide registration application, EPA assesses a variety of studies and considers product composition and use patterns to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the use of the pesticide product. Risk assessments are developed to evaluate how the pesticide product, including the active ingredient, might affect a range of nontarget organisms, including humans and terrestrial and aquatic wildlife (plants and animals). Based on these assessments, EPA evaluates and approves language for each pesticide label to ensure the directions for use, hazard statements, and other measures are appropriate to mitigate potential risk. In this way, the pesticide's label helps to communicate essential limitations and mitigations that are necessary for human health and environmental safety. In fact, under FIFRA, it is a violation to use a pesticide in a way that conflicts with the label.

As noted above, for the product at issue, EPA does not have an end-use product application in house to fully assess potential real-world exposures and risks associated with that product. As a result, EPA's analysis of potential risks is based on theoretical end-use products and potential exposure scenarios, levels, and durations in order to assess the potential for risk from use of this technical/MP product for formulation into future products. As stated above, any end-use products formulated with nootkatone would first need to be evaluated and registered by EPA before the product(s) can be sold or distributed.

3.1 Assessment of Risk to Human Health

To assess risks to human health from use of biochemical pesticides, EPA evaluates the potential toxicity of a product and the likelihood, amount, and types of exposure users and bystanders are likely to experience. In conducting a risk assessment, EPA must consider: (1) the hazards of a substance and (2) the exposure to that substance that a person will be exposed to as a consequence of use either directly or indirectly. EPA uses this combined information to assess and characterize the risk(s) and predict the probability, nature, and magnitude of the adverse health effects that may occur from use of the substance in the manner described. For nootkatone, EPA estimated exposures based on theoretical formulations and use patterns in order to assess potential human health risks from exposure to nootkatone.

When evaluating the toxicity of biochemical pesticides, EPA typically requires a range of Tier I data: acute toxicity data (acute oral toxicity, acute inhalation toxicity, acute dermal toxicity); irritation tests (primary eye irritation, primary dermal irritation and dermal sensitization); subchronic testing (90-day oral, 90-day dermal, 90-day inhalation); mutagenicity testing (bacterial reverse mutation test and *in vitro* mammalian cell assay) and developmental toxicity testing (prenatal development). Tier II and III testing is triggered only when there is indication, usually through lower tier testing, that a biochemical pesticide has unusual characteristics such as subchronic toxicity or is suspected or known to be a carcinogen. [40 CFR 158.2050].

Human health toxicity data requirements were satisfied for nootkatone with guideline toxicity studies. EPA will need additional information regarding potential exposure to the pesticide under the labeled use conditions and will complete that assessment when end products are submitted to the Agency for review.

3.1.1 Toxicological Data/Information

The toxicology database is used for assessing the potential toxicity of nootkatone. All of the acute toxicology data requirements for nootkatone were satisfied by guideline studies (acute oral toxicity (rat), acute dermal toxicity (rat), acute inhalation toxicity (rat), primary eye irritation (rabbit), primary dermal irritation (rabbit), and dermal sensitization (local lymph node assay - LLNA) using nootkatone as the test substance. The chemical is classified as having low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category IV). It is considered non-irritating to the eye (Toxicity Category IV), slightly irritating to the skin (Toxicity Category IV) and is not a dermal sensitizer. The Signal Word for the MP is “Caution.”

To satisfy the human health assessment data requirements, guideline subchronic toxicity studies were performed using nootkatone technical grade of the active ingredient (TGAI) as the test substance. The applicant submitted the following guideline subchronic toxicity studies: 90-day oral, 28-day dermal (in lieu of a 90-day dermal), 14-day inhalation dose range finding study, 90-day inhalation, prenatal developmental and genotoxicity data. Tier II and III studies have not been triggered at this time.

Findings from guideline studies for subchronic toxicity are as follows:

90-day oral: (870.3100)
The 90-day oral toxicity study identified no human-relevant adverse effects at the highest dose tested of 1000 mg/kg/day; therefore, an endpoint for dietary exposure was not selected. MRID 50447615

28-day dermal: (870.3200)
A dermal endpoint was selected based on clinical & histopathological findings of irritation (epithelial hyperplasia with occasional ulceration and/or hyperkeratosis) observed at the application site in the 28-day dermal toxicity study (NOAEL = 75 mg/kg/day; LOAEL = 300 mg/kg/day). No systemic effects via the dermal route were observed at the highest dose tested. The dermal loading rate from this study (minimum 99 mg ai/cm^2) was also used for risk assessment purposes where definitive exposures were known at the NOAEL. This approach was used because the applicant provided the loading rate for the skin applied repellent. MRID 50447617

14-day and 90-day inhalation: (870.3465)
An inhalation endpoint was selected based on observations of slight diffuse squamous metaplasia of the respiratory epithelium lining the ventral larynx in the 14-day dose-range finding inhalation toxicity study. Due to uncertainties regarding analysis of control atmospheres and tissue preservation methodology in the 90-day inhalation toxicity study and limitations with respect to the duration and number of animals used in the 14-day inhalation toxicity study, the Agency utilized both the 90-day and 14-day inhalation toxicity studies in the selection of the inhalation endpoint (NOAEC = 0.0484 mg/L; LOAEC = 0.0993 mg/L). MRID 50447619 & 20

Prenatal developmental: (870.3700)
There was no evidence of increased quantitative or qualitative fetal susceptibility in the prenatal developmental toxicity study in rats. There were no maternal or developmental effects up to the limit dose (1,000 mg/kg/day). MRID 50447622

Genotoxicity: (870.5100 & 5375)
Based on information from the *in vitro* studies, there was no evidence for genotoxicity. Additionally, in its assessment of nootkatone for use as an additive in animal feed, the European Food Safety Authority (EFSA) evaluated two genotoxicity studies for nootkatone (bacterial reverse mutation test and micronucleus assay in human lymphocytes), which were also negative for genotoxicity (EFSA, 2015). MRID 50447623 & 24

The toxicological endpoints used in the human health risk assessment are summarized in Table 1. In sum, dermal and inhalation endpoints were selected. No endpoint was selected for dietary exposure. No endpoint was selected for prenatal development studies as the substance is not developmentally toxic. There was no evidence of genotoxicity in the available *in vitro* studies.

Because human equivalent doses (HEDs) were calculated for the short- and intermediate-term inhalation endpoint, the interspecies extrapolation uncertainty safety factor was reduced to 3X, and the level of concern (LOC) for inhalation exposure is 30 (3X for interspecies extrapolation and 10X for intraspecies variation). Risk for each exposure scenario was calculated using a

margin of exposure (MOE), which is a ratio of the toxicological endpoint to exposure. For this assessment, dermal MOEs greater than 100 do not exceed the Agency's LOC, and inhalation MOEs greater than 30 do not exceed the Agency's level of concern (LOC).

Because residues of nootkatone are not expected in or on food commodities, the requirements of the Federal Food, Drug, and Cosmetic Act do not apply, including the retention of a children's safety factor.

During the public comment period, a commenter raised a question about the potential interaction between nootkatone, which is derived from grapefruit, and prescribed statins drugs. According to the FDA, grapefruit may affect the body's ability to process or utilize certain drugs, either by blocking enzymes or affecting transport of the drugs throughout the body. Available information indicates that nootkatone can inhibit certain enzymes, which may affect the body's ability to metabolize certain drugs, but how much enzyme inhibition occurs is likely to be dependent on how much nootkatone may be absorbed into the system[2]. In order to assess this potential risk from exposure to nootkatone through dermally applied insect repellents or ULV area-wide mosquitocide spray, EPA will need to evaluate the potential of nootkatone to interact with certain prescription and over-the-counter drugs when reviewing an application for registration of an end-use product for both dermally applied insect repellent and ULV area-wide mosquitocide uses. When reviewing future end-use products, EPA will evaluate each formulation to ensure they meet the FIFRA safety standard.

Table 1. Summary of Toxicological Doses and Endpoints for Nootkatone for Use in Human Health Risk Assessment

Exposure/Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	An endpoint attributable to a single exposure has not been identified.			
Chronic Dietary - For All Populations	An endpoint attributable to dietary exposure has not been identified. No human-relevant adverse effects were observed up to the limit dose in the available repeat-dose oral toxicity studies.			
Incidental Oral	An endpoint attributable to incidental oral exposure has not been identified.			

[2] Tassaneeyakul W, Guo L-Q, Fukuda K, Ohta T, Yamazoe YJAob, biophysics. Inhibition selectivity of grapefruit juice components on human cytochromes P450. 2000; 378:356-63; Fayz S, Inaba TJAa, chemotherapy. Zidovudine azido-reductase in human liver microsomes: activation by ethacrynic acid, dipyridamole, and indomethacin and inhibition by human immunodeficiency virus protease inhibitors. 1998;42:1654-8.

Table 1. Summary of Toxicological Doses and Endpoints for Nootkatone for Use in Human Health Risk Assessment				
Exposure/Scenario	**Point of Departure**	**Uncertainty Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1 day 6 months)	Dermal NOAEL= 75 mg/kg/day	UF_A = 10X UF_H = 10X	LOC for MOE = 100	28-day dermal toxicity (rat) Dermal NOAEL = 75 mg/kg/day Dermal LOAEL = 300 mg/kg/day based on clinical and histopathological findings of dermal irritation
Inhalation Short- and Intermediate-Term (1 day to 6 months)	Inhalation NOAEC = 0.0484 mg/L HEDs range from 0.16 mg/kg/day – 0.69 mg/kg/day*	UF_A = 3X UF_H = 10X	LOC for MOE = 30	14-day and 90-day inhalation toxicity (rat) Inhalation NOAEC = 0.0484 mg/L (90-day study) Inhalation LOAEC = 0.0993 mg/L based on slight diffuse squamous metaplasia of the epithelial lining of the ventral larynx

RfD = reference dose. **PAD** = population-adjusted dose. **NOAEL** = no-observed-adverse-effect-level. UF_A = interspecies uncertainty factor. UF_H = intraspecies uncertainty factor. **LOC** = level of concern. **MOE** = margin of exposure. **LOAEL** = lowest-observed-adverse-effect-level. **NOAEC** = no-observed-adverse-effect-concentration. **LOAEC** = lowest-observed-adverse-effect-concentration.

*More details on HEDs can be found in Table 2 of EPA Memorandum entitled "Occupational and Residential Exposure and Risk Considerations for a FIFRA Section 3 Registration of a Manufacturing Product Containing 99.4% Nootkatone" and dated 3/23/20.

3.1.2 Dietary exposures and risks

Dietary Exposure and Risk Characterization: A dietary risk assessment has not been conducted because the information submitted by the applicant assumed that products would not result in residues in or on food. Residues in or on food are not expected from a use as a dermally applied insect repellent, and in the theoretical scenarios presented by the technical/MP applicant, the ultra-low volume and low volume spray end-use product is intended to be applied in a manner that avoids drift to food/feed crops. See section 7 below for conditions of labeling that are required for the ultra-low volume/low volume spray product.

Drinking Water Exposure and Risk Characterization: A quantitative drinking water exposure assessment has not been conducted due to the lack of any toxicity associated with oral exposure. Based on the available information EPA cannot determine whether use of the product may result in residues in drinking water, but even if residues are in drinking water, it would not result in any risks of concern due to the lack of oral toxicity.

3.1.3 Occupational and Residential Exposure and Risk Assessment

A. Exploratory Assessment - Discussion

The ULV/LV use scenario is expected to result in occupational handler and residential post-application exposures. The insect repellent use scenario is expected to result in residential handler and residential post-application exposures. To assess potential end-use product user risk associated with products formulated with this technical/MP product, EPA conducted an exploratory assessment of the ULV/LV & dermally applied skin repellent scenarios suggested by the technical/MP applicant. EPA conducted separate occupational and residential assessments. They include: (1) occupational assessment for the ULV/LV exposure scenario; (2) residential handler assessment for the dermally applied skin repellent exposure scenario; (3) residential post-application assessment for the ULV/LV exposure scenario; and (4) residential post-application exposure assessment for the dermally applied insect repellent scenario.

1. Occupational Exposure

Because toxicological endpoints have been identified and occupational exposures are anticipated, exploratory quantitative short- and intermediate-term occupational handler exposure and risk assessments have been conducted. Risk for each exposure scenario, in this case, ULV/LV, has been calculated using an MOE, which is a ratio of the toxicological endpoint to exposure. For this assessment, dermal MOEs greater than 100 do not exceed the Agency's level of concern (LOC) and inhalation MOEs greater than 30 do not exceed the Agency's LOC, and therefore are not considered to be of concern. As a result of this assessment, the area ("low volume or ultra-low volume") spray for terrestrial nonfood use is anticipated to result in occupational handler exposure. Occupational exposures and risk estimates for the ULV/LV spray theoretical scenario end use patterns are summarized in Table 2 below.

Table 2. Occupational Exposure and Risk Estimates for Prototype Products Containing Nootkatone

Product	Exposure Scenario	Dermal MOE[1] (LOC = 100)	Inhalation MOE[1] (LOC = 100)
Low volume/ultra-low volume spray	M/L, Aerial, Broadcast, Vector control	910	8400
	M/L, Aerial, Broadcast, Forestry	190	1800
	M/L, Aerial, ULV/wide-area, Forestry	30 (no gloves) 180 (gloves)	280
	M/L, Aerial, ULV/wide-area, Vector control	30 (no gloves) 180 (gloves)	280
	M/L, Truck-mounted fogger/mister, ULV/wide-area, Vector control	76 (no gloves) 440 (gloves)	700
	M/L, Truck-mounted fogger/mister, Broadcast, Vector control	910	8400
	Applicator, Aerial, Broadcast, Vector control	96000	380000

Table 2. Occupational Exposure and Risk Estimates for Prototype Products Containing Nootkatone			
Product	**Exposure Scenario**	**Dermal MOE[1] (LOC = 100)**	**Inhalation MOE[1] (LOC = 100)**
Low volume/ultra-low volume spray	Applicator, Aerial, Broadcast, Forestry	20000	78000
	Applicator, Aerial, ULV/wide-area, Forestry	3200	13000
	Applicator, Aerial, ULV/wide-area, Vector control	3200	13000
	Applicator, Truck-mounted fogger/mister, ULV/wide-area, Vector control	1100	2300
	Applicator, Truck-mounted fogger/mister, Broadcast, Vector control	14000	27000

[1]MOEs derived based on baseline personal protective equipment (PPE): single layer clothing, no gloves and no respirator (unless otherwise noted).

2. Residential Handler & Residential Post Application Exposure

Because the information provided for each theoretical scenario did not contain the full suite of information typically present on an end-use product label, EPA in its exploratory assessment assumed some of the inputs for the exposure assessment. Based on the parameters of the theoretical scenarios provided (e.g., application rates, formulation concentration, application methods, use patterns, and use sites), EPA did not identify risks exceeding the Agency's LOC to residential handlers resulting from dermal and inhalation exposure to the dermally applied skin repellent product, nor did EPA identify any risks exceeding the Agency's LOC for post-application dermal or inhalation exposures for this product. For the ULV/LV spray product, EPA did not identify any residential post-application dermal or inhalation risks exceeding the Agency's LOC. Residential exposure and risk estimates for the dermally applied insect repellent and the ULV/LV spray theoretical scenario end-use patterns are summarized in Table 3 below.

Table 3. Residential Exposure and Risk Estimates for Prototype Products Containing Nootkatone			
Product	**Exposure Scenario**	**Dermal MOEs (LOC = 100)**	**Inhalation MOEs (LOC = 30)**
Dermally applied insect repellent	Handler	N/A[1]	1400
	Post-application	250[2]	N/A
Low volume/ultra-low volume spray	Post-application lawns and turf	840-82000	N/A

[1] N/A Not applicable to the exposure scenario

[2]The dermal MOE calculated for insect repellent is based on skin loading rate as prescribed in the materials submitted by the registrant indicating 0.4 mg ai/cm^2. This was compared to the loading rate in the dermal toxicity study at the NOAEL (minimum 99 mg ai/cm^2) from that study to calculate risks. Using the dermal loading approach is appropriate for assessing risks from a chemical that is not systemically toxic when information about dermal loading is available. In this instance, the registrant provided specific dermal loading information concerning the dermally applied insect repellent; without similar information for other use patterns, the Agency used a body burden approach based on the endpoint in the dermal toxicity study (NOAEL = 75 mg/kg/day).

For more information on the human health hazard assessment and the occupational and residential exposure assessment of nootkatone, please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0122" at http://www.regulations.gov).

3.2 Assessment of Ecological Exposure and Risk

To assess ecological risks from use of biochemical pesticides, EPA evaluates the likely environmental impacts as a result of exposure of the chemical to plants and animals in the environment and to whether that exposure will cause harm or ecological effects. EPA uses this combined information and considers the overall toxicity to characterize the risk(s) in order to identify what levels may cause harmful effects on the plants and animals of concern that may occur from use of the substance in the manner described.

On the toxicity side, EPA initially requires that a wide range of studies including Tier I testing be done on the following nontarget organisms: mammalian (acute, subchronic, prenatal developmental, and mutagenicity), birds (acute oral and dietary), fish (acute freshwater fish and aquatic invertebrates), plants, and insects. Testing is organized in a tiered structure, where Tier I studies test worst-case exposure scenarios and higher tiers (Tiers II and III) generally encompass definitive risk determinations and longer-term greenhouse or field testing. Higher tier testing is implemented only when unacceptable effects are seen at the Tier I screening level. All data requirements may be addressed with guideline studies or scientific rationales. For nootkatone, all nontarget toxicology data requirements have been satisfied per 40 CFR 158.2060 through acceptable guideline studies.

3.2.1 Terrestrial Animals and Plants

The overall risk profile of nootkatone is expected to be low based on the theoretical use scenarios, and risks to non-target organisms are not anticipated under the theoretical use scenarios provided.

Birds: (850.2100 & 850.2200)
Acute avian oral toxicity and avian dietary toxicity data requirements were satisfied by acceptable guideline studies. Nootkatone is practically nontoxic to birds when exposed to a single oral dose. The acute oral LD_{50} was >2250 mg/kg-bw. The 14-day NOAEL was 2250 mg/kg-bw. In the avian dietary toxicity study, nootkatone is identified as slightly toxic to birds. The acute dietary LC_{50} was determined to be > 6000 ppm ai (1360 mg ai/kg bw/day). The NOEC, based on decreased body weight and body weight-change, was less than 6000 ppm ai (<1360 mg ai/kg-bw/day). A second guideline acute avian dietary toxicity study was submitted for nootkatone; the results of the study indicate that the active ingredient is slightly toxic to birds acute dietary LC_{50} was greater than 6000 ppm ai (3404 mg ai/kg-bw/day). The NOEC was 6000 ppm ai (3404 mg ai/kg-bw/day). MRID 50447628,29 & 30

Nontarget Insects: (880.4350 & 850.2200)
A guideline nontarget honeybee acute contact toxicity study indicates that nootkatone is practically nontoxic to honeybees and other nontarget insects. The 48-hour LD_{50} was > 100 µg ai/bee, and the NOEC was 100 µg ai/bee. MRID 50447631

Nontarget Plants: (880.4100& 880.4150)
Eight of the ten species of terrestrial plants were adversely affected when sprayed with nootkatone in nontarget plant testing. The EC_{25} for dry weight for dicots and monocots was 3.5 and 5.9 lb a.i./A (pounds active ingredient per acre), respectively, and the NOAEC for dicots and

monocots was 1.1 and 2.2 lb a.i./A, respectively. Applications by aerial and ground equipment, which had assumed a maximum application rate of 0.12 lb a.i./A, are not anticipated to result in any adverse effects. Risk quotients for listed plant species under these scenarios were < 0.1, which is well below the Agency's level of concern of 1.0. MRID 50447632 & 33

3.2.2 Aquatic Organisms

Freshwater Fish and Aquatic Invertebrates: (850.1075 & 850.1010)
Nootkatone is classified as slightly to moderately toxic to invertebrates and fish (EC_{50}s of 12 and 3.7 mg/L, respectively). Drift from both ground and aerial applications at a rate of 0.12 lb a.i./A into water bodies is not anticipated to be sufficient to result in any adverse effects. MRID 50447626 & 27

3.2.3 Endangered Species Conclusion

Nootkatone is practically non-toxic to birds, mammals, and bees and nootkatone is not expected to pose a risk to aquatic organisms at any of the application rates or methods. Furthermore, the overall risk profile of nootkatone is expected to be low and risks to non-target organisms are not anticipated under the theoretical use scenarios provided. As a result of the overall low toxicity profile and limited exposure from the theoretical scenarios, the EPA is able to the make a "no effect" determination for direct and indirect effects to federally listed threatened and endangered and their designated critical habitats.

The database of toxicity studies required to support the risk assessment to the environment is complete. For more information on the environmental theoretical risk assessment of nootkatone, please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0122" at http://www.regulations.gov).

4. Benefits

By definition, biochemical pesticides are favorable when compared to currently registered conventional pesticide alternatives because biochemicals are naturally occurring substances (or substances structurally similar and functionally identical to naturally occurring substances) with a history of exposure to humans and the environment demonstrating minimal toxicity and a nontoxic mode of action to the target pest(s). Benefits of biochemical & biochemical-like pesticides as compared to conventional pesticides typically include lower toxicity profiles for humans and nontarget organisms and faster degradation in the environment.

For nootkatone, while the registration would be limited to a manufacturing-use product, nootkatone has the potential for being used in future end-use products that are intended to be used as insect repellent for ticks, mosquitoes, and a wide variety of other biting pests as well as an adulticide for mosquitoes. In many areas of the United States, mosquitoes have become resistant to currently available insecticides; a new active ingredient available in the toolbox will help vector-control programs. Mosquito-borne and tickborne diseases are a growing threat in every US state and territory. The number of reported cases of mosquito-borne and tickborne diseases doubled from 2004-2018. Tickborne diseases represent almost 8 in 10 of all reported

vector-borne disease cases in the United States. Increasing risk from these diseases means increasing demands on federal, state, and local health departments and vector control agencies. In any case, it is expected that the use of nootkatone might reduce the hazards to both users and wildlife associated with the use of conventional insecticides.

5. Public Comments

On Monday, October 15, 2018, EPA announced receipt of an application in the *Federal Register* to register an MP, Nootkatone (EPA File Symbol 91873-R), containing the new active ingredient Nootkatone (83 FR 519412). No substantive comments were received in response to this Notice of Receipt.

Because the pesticide product contains a new active ingredient, nootkatone, EPA opened a 15-day public comment period on June 30, 2020. The comment period closed July 14, 2020. EPA took this action in accordance with a policy, first implemented in October 2009, designed to provide a more meaningful opportunity for the public to participate in major registration actions. Two comments were received as a part of that process. One comment expressed concerns about nootkatone, which, because it is found in grapefruit, raises a concern for those people who might use the insect repellent product and also take prescribed statin drugs, which have a warning about the consumption of grapefruit or grapefruit juice while taking these statin drugs. The second comment stated that EPA identified a subchronic inhalation toxicity data gap and urged EPA to work with the applicant to satisfy this data requirement using a non-animal, weight-of-evidence approach.

EPA response to comment #1: Grapefruit is known to interact with certain medications by blocking the action of an enzyme in the liver named cytochrome P450 3A4 (CYP3A4), which helps to break down some medications. Due to enzyme inhibition, larger than normal amounts of the medication, including some statin drugs, are left in the body. For this reason, the FDA has required that some prescription and over-the-counter (OTC) drugs taken by mouth, including statin drugs, include warnings against drinking grapefruit juice or eating grapefruit while taking the drug and healthcare providers commonly counsel patients to avoid taking certain medications with grapefruit juice or other grapefruit products. https://www.fda.gov/consumers/consumer-updates/grapefruit-juice-and-some-drugs-dont-mix

Available information indicates that nootkatone, although it is naturally found in grapefruit, does not appear to inhibit the CYP3A4 enzyme but that it can inhibit two other enzymes - Cytochrome P450 2A6 and 2C19 (CYP2A6 and CYP2C19). These enzymes metabolize different medications than the CYP3A4 enzyme, and thus, there remains a potential for nootkatone to interact with drugs. The extent to which nootkatone may potentially interact with different prescription or OTC drugs will depend on the rate of dermal absorption and the ability of nootkatone to affect the metabolism of these enzymes.

EPA is concerned with the amount of nootkatone that may be absorbed into the body systemically through the use of the dermally applied insect repellent or ULV area-wide mosquitocide spray. As a general matter, depending on the substance's chemical characteristics,

a portion may be able to pass through the skin barrier and enter the systemic circulation of the body. Researchers can either predict the amount of systemic absorption through modeling or directly measure absorption through experimental testing. At this time however, there are no published/reported research to determine an accurate amount of nootkatone that enters the body through the skin. The inhibition of the enzymes is dose dependent, meaning more nootkatone in the body may cause more inhibition. Given the uncertainty in the degree of nootkatone that can absorb through the skin and enter the body and the many medications metabolized by the CYP2A6 and CYP2C19 enzymes, EPA will fully assess this potential risk posed by any dermally applied insect repellent and ULV area-wide mosquitocide spray when end-use product formulations are submitted to the Agency for registration. Specific product formulations may have an impact on the absorption rate; therefore, product-specific data to evaluate those potential risks will be required, including dermal absorption data and *in vitro* metabolism data as described in Section 8. This requirement will be added as an amendment to the manufacturing use product label and registration notice. Prior to the submission of any application for an end-use product(s), registrants are recommended to meet with the EPA to discuss the appropriate protocols to be used.

EPA continues to conclude that the nootkatone manufacturing-use product can be registered. Because the potential risk from interaction with drugs will be contingent on the submission and review of required data to support end-use products, EPA concludes that the manufacturing-use product will not cause unreasonable adverse effects on the environment, as long as it is used for the formulation of end-use products that are demonstrated not to pose unreasonable adverse effects, including to people taking certain prescription or OTC drugs. As EPA noted above, this potential risk will be considered as part of the unreasonable adverse effects finding for any end-use product seeking registration.

EPA response to comment #2: An inhalation endpoint was selected based on both the 90-day and 14-day inhalation toxicity studies. That endpoint was included in the human health risk assessment, which was available for public view during the comment period. This data requirement has been satisfied, and there is no data gap. Specific information, including the document addressing this comment is located in the docket and can be found at docket www.regulations.gov (search for "EPA-HQ-OPP-2018-0122").

6. Regulatory Decision

The nootkatone database for the technical/MP product is considered to be complete with regard to the human health and environmental fate data requirements.

Based on the information submitted about potential use patterns of future end-use products, EPA has conducted an exploratory assessment to evaluate whether use of this MP under those conditions for use associated with the theoretical end-use products meet the standard for FIFRA registration, i.e., they would not cause unreasonable adverse effects on the environment when used as intended.

EPA has determined that the dermally applied insect repellent and the low-volume/ultra-low-volume spray uses of the technical/MP product meet the standard for registration under FIFRA, when used in accordance with the parameters described in section 7 of this document. Again, such end-use products would first need to be evaluated and registered by EPA before the product(s) are sold or distributed.

As indicated in the parameters described in section 7, applications for section 3 registration of a dermally applied insect repellent product and an ULV/LV spray treatment product will require additional product specific end-use data to be submitted and reviewed by EPA. See section 8 of this document for further information.

For this reason, EPA is granting the unconditional registration of the Technical/MP under Section 3(c)(5) of FIFRA, with labeling restricting use only for formulation into certain end-use products. Applications for those end-use products must be submitted for consideration for registration and must meet the standards for registration, be supported by necessary data, including efficacy data, and restrict uses as prescribed by EPA in the MP label. See section 7 for specific restrictions. EPA is taking this action based solely on assumptions of exposure anticipated from theoretical end-use products, in the absence of end-use product specific data/information to assess the risks and benefits of any of end-use product actually associated with this manufacturing use product, which would allow the EPA to conduct a full assessment of the risks and benefits of both products.

One product is being registered: A Manufacturing-use product (MP), Nootkatone (EPA File Symbol 91873-R), containing the new active ingredient, nootkatone.

7. Labeling Requirements

The label for the registered MP product must include the following statement and directions for use:

Using this product for formulation into other pesticide products is prohibited, unless the product meets both of the following conditions:

1) This product may be used for formulation only into end-use products for which all necessary end-use product-specific data have been provided and support registration for the end-use product. Necessary end-use product-specific data include, but are not limited to, efficacy data; *in vitro* metabolism data; and dermal absorption data. Potential registrants of end-use products are encouraged to meet with EPA to discuss data necessary to support registration of such products prior to submitting applications for registration.

2) This product may be used for formulation only into end-use products intended for the following uses that meet the following conditions:

    a) For end-use products with directions for use as dermally applied insect repellents, the product:

i. can contain no more than 20% active ingredient in the end-use product formulation;
ii. cannot be applied more than four times per day; and
iii. the maximum application rate cannot exceed 0.4 mg of Nootkatone/cm^2 skin per day.

b) For end-use products with directions for use as low volume and ultra-low-volume sprays, the product:

i. can contain no more than 60% active ingredient in the end-use formulation;
ii. may be applied only via vehicle mounted ground spray and fixed wing rotary aerial spray at a maximum application rate up to 3 oz/acre at 60% nootkatone equivalent to up to 55 g Nootkatone/acre (0.12 lbs ai/acre);
iii. for mixers/loaders, product must be applied using PPE; waterproof gloves or nitrile gloves required;
iv. application frequency may be on an as needed, targeted basis; and
v. the end-use product label must:
    1) either prohibit use that results in direct or indirect residues of product in or on food crops or
    2) residues in or on food from use of this product must be covered by a tolerance or exemption. A petition to establish such a tolerance or exemption must be submitted and approved by EPA under section 408 of the FFDCA, or EPA must confirm that an existing tolerance or exemption already covers such residues.

8. Future Data Requirements

For the uses described above in section 7 of this document in association with the MP product, EPA has not identified risks exceeding EPA's levels of concern. The following future actions will need to occur before end-use products meeting the parameters for those uses can be registered and the technical/MP product label amended, if needed.

In order to determine whether to register an end-use product(s) formulated from this MP product, EPA would need to review all product-specific data, including efficacy data, *in vitro* metabolism data and dermal absorption data that EPA determines is necessary to support registration of the end-use product(s). Efficacy data supporting skin-applied repellents often involves testing involving intentional exposure of human subjects, as outlined in OSCPP guideline 810.3700. In that case, requirements of EPA's Human Studies Rule (40 CFR part 26, subparts K-L) would apply, requiring the submission of a protocol and review by EPA and the Human Studies Review Board, prior to initiation of such study. A protocol for a study concerning the efficacy of the ULV/LV use would also be recommended to be submitted for EPA review prior to initiation of the study. To assess the potential for nootkatone to interact with various drugs, EPA will require dermal absorption data for the end-use product formulation and *in vitro* metabolism data on potential drug interactions. EPA will accept *in vitro* dermal absorption data in human tissues tested according to OECD Guideline 428 (https://www.oecd-ilibrary.org/environment/test-no-428-skin-absorption-in-vitro-method_9789264071087-en). A protocol to be used for the human

in vitro metabolism study will need to be developed. EPA recommends using guidance from FDA's Center for Drug Evaluation and Research entitled "In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, Guidance for Industry" (Section III , Evaluating Metabolism-Mediated Drug Interactions; https://www.fda.gov/media/134581/download). It is recommended that an end-use applicant meet with EPA in advance of the submission of any end-use product application in order to ensure that all data requirements for the end-use product have been identified and data will be provided in accordance with approved protocols. If any end-use product application seeks uses that differ from what EPA is proposing to register in this document, EPA would need to conduct new risk assessments for those applications.

All assessments including the product label supporting this decision can be found in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0122" at www.regulations.gov).