UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 20-MAR-2020

SUBJECT: **Rotenone:** Human Health Risk Assessment for Registration Review.

PC Code: 071003
Decision No.: 560158
Petition No.: NA
Risk Assessment Type: Human Health Risk Assessment
TXR No.: NA
MRID No.: NA

DP Barcode: D456553
Registration No.: see Section 3.3
Regulatory Action: Registration Review
Case No.: 0255

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As part of Registration Review, PRD of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary, occupational, and residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of rotenone. This memorandum serves as HED's draft human health risk assessment of the dietary, occupational, and residential exposure; and combined risk from the registered uses of rotenone. The most recent quantitative human health risk assessment was performed in 2006 (C. Smith, D328478, 06/28/2006) followed by a Section 18 assessment in 2014 (M. Sahafeyan et al., D421308, 08/07/2014). The following risk assessment updates have been made:

- Updated dietary, residential, and non-occupational bystander exposure assessments were completed to reflect recent updates to HED's Standard Operating Procedures (SOPs)/policies.

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1.0 Executive Summary

The Health Effects Division (HED) has conducted a human health draft risk assessment (DRA) to evaluate all existing registrations of the active ingredient (ai) rotenone ((2*R*,6a*S*,12a*S*)-1,2,12,12a-tetrahydro-8,9-dimethoxy-2-(1-methylethenyl)[1]benzopyrano[3,4-*b*]furo[2,3-*h*][1]benzopyran-6(6a*H*)-one). Rotenone is a naturally occurring compound that is present in a number of plants. Rotenone is applied directly to water to manage fish populations in lakes, ponds, reservoirs, rivers, and streams. Currently, rotenone is used as a piscicide in two main areas. The first use is when rotenone is used in water body (lakes, ponds, streams, *etc.*) fish management strategies. Rotenone is typically used in this manner when a water body has an unbalanced fish population or a non-native introduced species threatens native fish populations. The second use is when rotenone is used in catfish aquaculture. The use of rotenone in catfish aquaculture is typically limited to treatment of the aquaculture ponds in the spring prior to stocking of a new "crop" of catfish fry. The purpose of this treatment is to eliminate undesirable fish species (*i.e.*, shad, blue gills, and mud cats) that would compete with the catfish fry. There are no tolerances required or established for residues of rotenone in fish or any crops.

Use Profile
Piscicidal applications of rotenone are applied using several types of application equipment – including helicopters, closed system aspirators, boats with over-surface booms, boats with underwater hoses, drip bars (in rivers and streams), and backpack sprayers. Occupational handlers are required to wear coveralls, long-sleeved shirt, long pants, chemical resistant shoes plus socks, chemical-resistant gloves, and a dust/mist filtering respirator. Rotenone is a restricted use pesticide (RUP). HED notes that rotenone is applied by highly-trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water). The SOP Manual can be found at https://units.fisheries.org/rotenone-stewardship/. There are no existing or proposed direct residential uses for rotenone.

Exposure Profile
Humans may be exposed to rotenone in drinking water since rotenone may be applied directly to bodies of water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application as well as during and after the application. It is unlikely for occupational workers to come into contact with previously treated water except for water sample and dead fish collection. HED does not have data to assess these occupational post-application activities, which are assumed to be negligible when compared to the occupational handler exposure scenarios. As a result, no separate assessment was completed for the occupational post-application exposure. There are no existing or proposed direct residential uses; however, a residential post-application assessment has been conducted for individuals swimming or fishing in treated waterways. Non-occupational exposure resulting from spray drift from aerial piscicidal applications onto residential areas may also occur.

For rotenone, based on the uses, short- and intermediate-term dermal and inhalation and dermal exposure is expected for occupational handlers. For the residential post-application swimming scenario, short-term dermal, inhalation, and incidental ingestion is anticipated for both adults and children (3 to < 6 years old).

Hazard Characterization & Dose Response Assessment
The toxicity database for rotenone is incomplete, as required by the 2007 revised 40 CFR Toxicology Data Requirements, however, it is sufficient for risk assessment purposes. The incomplete toxicological data identified include the following: subchronic inhalation neurotoxicity study, developmental toxicity study (rabbit), acute and subchronic neurotoxicity studies, immunotoxicity study, and subchronic (90-day) dermal study. In 2006, an additional database uncertainty factor (UF) of 10X was applied to account for database uncertainty. HED recommends to maintain the 10X database uncertainty factor at this time.

The most common effect in subchronic or chronic rat, dog, mouse, and/or hamster oral studies, is decreased body weight and/or body weight gain. Rats and dogs appear to be equally sensitive and both are more sensitive than mice or hamsters; females appear to be more sensitive than males to effects on body weight. No conclusions can be reached for either dermal or inhalation routes of administration since route specific data is not available for these routes of exposure. In the developmental studies, maternal toxicity occurred either at lower doses (rats) or at an equivalent dose in mouse maternal animals and the pups; no study was available on a non-rodent species. In a two-generation reproductive toxicity study (rat), adult and offspring toxicity were observed at doses greater than 3.0 mg/kg/day. The main effect in both parental animals and pups was decreased body weight and body weight gain. At this time, no quantitative or qualitative evidence supports increased susceptibility of rat or mouse fetuses or rat offspring.

An appropriate acute endpoint for the general population, including infants and children, was not identified in the available toxicity studies. The acute dietary risk estimate calculated for females 13-49 years of age is based on a no-observed-adverse-effect-level (NOAEL) of 15 mg/kg/day from the mouse developmental study. The chronic dietary risk estimated was derived from the NOAEL of 0.375 mg/kg/day in the chronic/carcinogenicity rat study. The short- and intermediate-term (non-cancer) incidental, dermal, and inhalation endpoints for occupational and residential risk assessment for rotenone is based on a NOAEL of 0.5 mg/kg/day from a reproduction study with a dermal absorption factor of 10 percent selected. Long-term exposure to rotenone is not expected for current registered uses. The dermal, inhalation, and incidental oral margins of exposure were combined for the rotenone risk assessment because the endpoints are based on the same toxicological effects. Effects were seen in both male and females so the body weight of an average adult (i.e., 80 kg) was used to estimate exposure. Due to data gaps in the toxicology database, an additional 10X UF was applied in the 2006 assessment to the various points of departure (PODs) selected. HED recommends maintaining the 10X database uncertainty factor at this time.

No evidence for carcinogenicity was seen in mice or rats and it is not mutagenic *in vitro* or *in vivo*. Therefore, rotenone is classified as Group E (evidence of non-carcinogenicity for humans) (Memo, R. Gardner, TXR 0052673, 10/05/1988).

In acute oral and inhalation studies, rotenone is severely toxic (Toxicity Category I). It is not toxic dermally (Toxicity Category IV) nor causes eye or dermal irritation (Toxicity Category IV), and it is also not a dermal sensitizer.

Residue Chemistry
The residue chemistry database is considered complete. There are no currently registered food uses for rotenone; therefore, residue chemistry data are not required for rotenone at this time. The rotenone fisheries management guideline manual has mandatory restrictions and SOPs to prevent consumption of treated fish. Rotenone is exempt from the need to establish tolerances because there are no U.S. registrations for use of rotenone, derris, or cube roots on food commodities as of March 23, 2011 (40 CFR §180.905 (b)).

Dietary Exposure Assessment
Two updated acute dietary exposure and risk assessments were conducted for rotenone. One assessment used the acute estimated drinking water concentration (EDWC) of 40 µg/L which reflects specifications in the SOP Manual that users be advised against the consumption of water until this level was reached and the other assessment used an EDWC of 200 µg/L provided by the Environmental Fate and Effects Division (EFED) which reflects the limit of solubility and maximum application rate for the majority of the labels for characterization purposes. Additionally, both assessments included a theoretical point estimate for freshwater finfish (wild and farm-raised). Although acute consumption of rotenone residues from fish is unlikely, HED has conducted highly conservative acute dietary exposure assessments to address the scenario where fish survive the treatment process and are consumed. The acute dietary exposure assessments were performed for rotenone for females 13-49 years of age, the only population subgroup for which an acute dietary endpoint was identified. The resulting acute dietary exposure estimates using EDWCs of 40 µg/L and 200 µg/L were 17% and 84%, respectively, of the acute population-adjusted dose (aPAD) at the 95th percentile of exposure and are not of concern. Based on the use pattern and restrictions, long-term consumption of fish or drinking water bearing residues of rotenone is extremely unlikely. Therefore, HED has determined that a quantitative chronic dietary exposure assessment is not necessary at this time.

Residential Exposure and Risk Assessment
There are no registered or proposed direct uses for residential handlers at this time for rotenone. There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with rotenone. Individuals can be exposed while swimming in treated waters by the dermal, incidental oral, and inhalation routes of exposure. The standard operating procedure to assess the residential swimming scenario has been updated since the time of the 2006 human health risk assessment (D328478), in addition, the concentration limit of 90 ppb has also since been implemented through placarding and restricted access. For this reason, the residential post-application swimming scenario has been updated for the purposes of registration review. There are no residential post-application exposure scenarios of concern with Margins of Exposure (MOEs) ranging from 2,100 to 41,000 (MOE > LOC of 1,000).

Combined Risk Assessment
Food Quality Protection Act (FQPA) considerations do not apply to rotenone for the currently registered (non-food) use patterns described in this risk assessment; however, HED did consider a combined assessment to account for potential exposures from residential and dietary exposures. The acute combined assessment is equivalent to the acute dietary exposure and risk estimates and is not of concern. Based on the use pattern and label restrictions, chronic dietary exposure to

rotenone is not anticipated; therefore, the short-term combined assessment is equivalent to the residential post-application exposure assessment and is not of concern.

Non-Occupational Spray Drift Assessment
The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Rotenone is used on flowing and non-flowing water to manage fish populations and can be applied via aerial equipment. The recommended drift scenario screening level is based on the use of the AgDrift Tier 1 aerial option. The drift assessment results in risk estimates of concern.

Occupational Exposure and Risk Assessment
Short-term and intermediate-term exposure is expected for the occupational handlers for rotenone. Occupational handlers are expected to be exposed by dermal and inhalation routes of exposure. Piscicidal applications of rotenone are applied using several types of application equipment – including helicopters, closed system aspirators, boats with over-surface booms, boats with underwater hoses, drip bars (in rivers and streams), and backpack sprayers. Occupational handlers are required to wear coveralls, long-sleeved shirt, long pants, chemical resistant shoes plus socks, chemical-resistant gloves, and a dust/mist filtering respirator. Rotenone is a restricted use pesticide (RUP). It is unlikely for occupational workers to come into contact with previously treated water except for water sampling and dead fish collection. Tasks after an application require the same label-specified PPE as handlers if the rotenone application is >90 ppb, such as deactivating with potassium permanganate, handling dilute rotenone solutions (*i.e.*, testing rotenone-treated water), and other post-application tasks. HED does not have data to assess these activities, which are assumed to be negligible when compared to the occupational handler exposure scenarios. All occupational exposures are reflected by the handler assessment therefore a separate post-application assessment is not conducted.

HED notes that rotenone is applied by trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water). The SOP Manual can be found at https://units.fisheries.org/rotenone-stewardship/.

The occupational use patterns have not changed since the 2006 Final HED Chapter of the Reregistration Eligibility Decision Document (RED) (D328478). While individual inputs of unit exposures and amounts handled may have been updated, the toxicological database and points of departure have not changed, therefore the overall risk picture for rotenone RUP uses remains consistent. For this reason, the occupational handler assessment was not revised for the purposes of Registration Review. Based on the two previous assessments (D328478 and D421308), occupational risk estimates are driven by the dermal route of exposure and result in combined risk estimates less than the target level of concern of 1,000 (MOEs < LOC = 1,000) for many of the scenarios. This continues to be the risk conclusions for the registered uses of rotenone.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied (see Appendix C).

2.0 Risk Assessment Conclusions

Based on the updated assessments, there are no risks of concern for residential post-application exposures and there are no dietary risk estimates of concern. All spray drift scenarios for aerial applications of rotenone are of concern at the edge of the treated area, however, although aerial applications are still allowed on the label, these application methods are unlikely to be supported in the future.

Although previous assessments identified several occupational handler risk estimates of concern at the label-required PPE and engineering controls, rotenone is a restricted-use pesticide with extensive training and requirements. It is applied by trained applicators who are required to follow a detailed SOP with explicit instructions regarding the application and post-application processes, all of which are anticipated to decrease the likelihood of applicator and post-application exposures. Even though there are extensive application restrictions in place, the occupational assessment had previously identified risks of concern for multiple application scenarios; therefore, the submission of additional toxicity studies are not anticipated to change the overall risk assessment conclusions and are not required at this time. HED recommends maintaining the 10X database uncertainty factor at this time.

2.1 Data Deficiencies

None.

2.1.1 Recommended and Established Tolerances

There are no established or required tolerances for residues of rotenone since it is not currently registered for use on food or feed items.

2.2 Label Recommendations

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

2.2.1 Recommendations from Residue Reviews

None.

2.2.2 Recommendations from Residential Assessment

None.

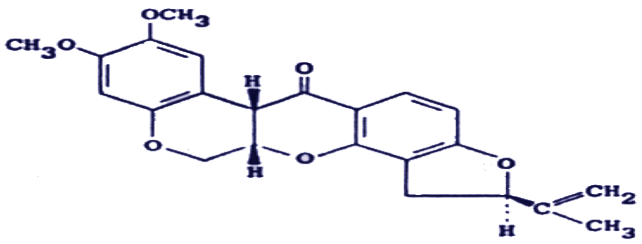
2.2.3 Recommendations from Occupational Assessment

Personal protective equipment (PPE), reference to the Rotenone SOP Manual[2], and updated re-entry information were not provided on one rotenone label (EPA Reg. No. 19713-316). The American Fisheries website which directs to the Rotenone SOP Manual and provides additional guidance on the safe and effective uses of rotenone products located on label(s) 89459-23 and 89459-32 is incorrect and should be updated to https://units.fisheries.org/rotenone-stewardship/.

3.0 Introduction

3.1 Chemical Identity

Table 3.1: Test Compound Nomenclature

Chemical structure	
Empirical formula	C_{23} H_{22} O_6
Common name	Rotenone
IUPAC name	(2R,6aS,12aS)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-b]furo[2,3-h]chromen-6-one.
CAS Registry Number	83-79-4
Chemical Class	Rotenoid
Known Impurities of Concern	Extraction compounds such as trichloroethylene & toluene in unspecified amounts[3]

[2] https://units.fisheries.org/rotenone-stewardship/sop-manual/rotenone-sop-manual-2nd-edition/

[3] The EPA's Office of Water has established maximum concentration levels (MCL) for trichloroethylene (5 ppb) and toluene 2000 ppb). However, recent environmental incidents have shown trichloroethylene levels to exceed the MCL after applications of rotenone to bodies of water. Most current CSFs either do not list or do not quantify the impurities. Therefore, HED is unable to conduct a qualitative or quantitative assessment of the potential risks posed by the impurities that may be present by any route of exposure.

3.2 Physical/Chemical Characteristics

Rotenone is a powder compound with a melting point of 160 -163 °C. Rotenone has a partition coefficient (n-octanol /water) of K_{ow} Log P = 4.16. The full complement of physiochemical properties for rotenone is provided in Appendix B.

3.3 Pesticide Use Pattern

The rotenone end-use products are Drexel 7.4% Rotenone Wettable Powder (EPA Reg. No. 19713-316), Prenfish Toxicant (EPA Reg. No. 89459-23), Rotenone Fish Toxicant Powder (EPA Reg. No. 89459-32), CFT Legumine Fish Toxicant (EPA Reg. No. 89459-48), and RF2232 Liquid FT (EPA Reg. No. 89459-85). For certain labels (EPA Reg. Nos. 89459-23, 89459-48, 89459-85), a closed system or semi-closed probe system must be used, if it is packaged in containers > 5 gallons. The formulator products are Cube Powder (EPA Reg. No. 89459-13), Cube Resins (EPA Reg. No. 89459-15), and Brittle Extract of Cube Root (EPA Reg. No. 89459-43). Formulator products are only used for the formulation and repackaging of piscicide end-use products.

In addition to the labeled requirements, registered rotenone labels also direct handlers to the Rotenone SOP Manual[4]. HED notes that rotenone is applied by highly-trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water). The SOP Manual can be found at https://units.fisheries.org/rotenone-stewardship/, which details specific procedures on how to minimize nontarget exposure and effects and to provide guidance on the complex label uses.

Table 3.3. Summary of Directions for Use of Rotenone.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/acre-foot)	Max. No. Applic. per Season[1]	Max. Seasonal Applic. Rate (lb ai/acre-foot)	Re-entry Restriction[2] (days)	Use Directions and Limitations
Non-Flowing Water (Lakes, Ponds, Reservoirs)						
Bag tow, aerial, metered drip system, submerged hose, boom sprayer (boat), backpack, mechanically-pressurized handgun, pour in/on	Drexel 7.4% Rotenone Wettable Powder, Wettable Powder [EPA Reg. No. 19713-316]	0.68 lb ai/acre-ft or 0.000016 lb ai/ft^3	2	1.36 lb ai/acre-ft	3 days post 250 ppb application	Do not use treated water to irrigate crops or release within 0.5 mi upstream of a potable water or irrigation water intake Do not use dead fish as food or feed
Bag tow, submerged hose, boom sprayer (boat),	Rotenone Fish Toxicant Powder,	0.54 lb ai/acre-ft		1.08 lb ai/acre-ft	2 days post 200 ppb application	Do not use treated water to irrigate crops or release within 0.5 mi upstream of a

[4] https://units.fisheries.org/rotenone-stewardship/sop-manual/rotenone-sop-manual-2nd-edition/ and https://units.fisheries.org/rotenone-stewardship/

Table 3.3. Summary of Directions for Use of Rotenone.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/acre-foot)	Max. No. Applic. per Season[1]	Max. Seasonal Applic. Rate (lb ai/acre-foot)	Re-entry Restriction[2] (days)	Use Directions and Limitations
mechanically-pressurized handgun, pour in/on	Wettable Powder [EPA Reg. No. 89459-32]					potable water or irrigation water intake Do not use dead fish as food or feed Applications with an aircraft, backpack sprayer, and drip can are prohibited.
Flowing Water (Lakes, Ponds, Reservoirs, Rivers, Streams)						
Bag tow, aerial, metered drip system, submerged hose, boom sprayer (boat), backpack, mechanically-pressurized handgun, pour in/on	Prenfish Toxicant, Liquid [EPA Reg. No. 89459-23] CFT Legumine Fish Toxicant, Liquid [EPA Reg. No. 89459-48] RF2232 Liquid FT, Liquid [EPA Reg. No. 89459-85]	0.56 lb ai/acre-ft or 0.000013 lb ai/ft^3 or 0.35 lb ai/cfs	2	1.12 lb ai/acre-ft or 0.000026 lb ai/ft^3 or 0.7 lb ai/cfs	2 days post 200 ppb application	Do not use treated water to irrigate crops or release within 0.5 mi upstream of a potable water or irrigation water intake Do not use dead fish as food or feed Do not apply when wind speeds are > 12 miles per hour.

[1] Maximum of two applications of rotenone per year taken from previous memo (C. Smith, D328776, 06/28/2006).
[2] The re-entry restriction was determined from the time it takes for the rotenone to dissipate to 90 ppb. Dissipation to 90 ppb from 200 ppb takes approximately 2 days and from 250 ppb takes approximately 3 days. (C. Smith, D328776, 06/28/2006).

3.4 Anticipated Exposure Pathways

Humans may be exposed to rotenone in drinking water, since rotenone may be applied directly surface water sources of drinking water. There are no residential handler uses of rotenone. However, there is the potential for residential post-application exposures for both adults and children from contact with previously treated water. Humans may be exposed to rotenone from swimming or fishing in previously treater water, since rotenone is applied directly to waterways. Non-occupational exposure to rotenone via spray drift is possible. Occupational exposures are expected from the application (dermal and inhalation) of rotenone, but not from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all of the uses of rotenone.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this

human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicity database for rotenone is incomplete, as required by the 2007 revised 40 CFR Toxicology Data Requirements, however, it is sufficient for risk assessment purposes. The incomplete toxicological data identified include the following: subchronic inhalation neurotoxicity study, developmental toxicity study (rabbit), acute and subchronic neurotoxicity studies, immunotoxicity study, and subchronic (90-day) dermal study. Based on a weight of evidence approach, considering all the available hazard and exposure data for rotenone, the Hazard and Science Policy Council (HASPOC) (J. Leonard, TXR 0058000, 03/20/2020) recommended that the subchronic inhalation study with neurotoxicity parameters and the developmental toxicity study (rabbit) remain required studies at this time if exposure is determined to be significant. The HASPOC recommended that the acute and subchronic neurotoxicity studies, immunotoxicity study, and subchronic (90-day) dermal study for rotenone be waived. However, if the use pattern were to change such that significant exposure is expected, then the Agency may revisit this conclusion. Rotenone is applied by trained applicators who are required to follow an SOP manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water).

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

There are no guideline metabolism studies available for rotenone. However, an Acceptable/Non-guideline metabolism and pharmacokinetics study is available for rotenone (rat). The primary

route of excretion was in the feces with polar metabolites being identified in the feces. Metabolic profiles for the seven metabolites found in the feces were not obtained. In conjunction with fecal elimination, rotenone underwent extensive enterohepatic circulation. Tissue accumulation was low, typically less than 1% of the administered dose.

4.2.1 Dermal Absorption

A dermal penetration study has not been submitted. Two suitable acute dermal toxicity studies in the rabbit are available for examination. In a dermal study with rotenone technical (97% a.i.), rotenone was applied as a single dose (5 g/kg) as light-yellow crystals with no vehicle (not moistened). No mortalities or evidence of systemic toxicity were observed to rabbits of up to 5 g/kg (MRID 43907501). Slight erythema seen at the application site cleared within 24 hours. These results suggest negligible dermal absorption of rotenone. In the second acute dermal study (MRID 44336402) with rotenone, brittle extract (rotenone 44.2%, other associated resins 44.2%, inerts 11.6%) test material was applied moistened with deionized water (0.952 mL/2020 mg of test material). There were no deaths with the LD_{50} > 2020 mg/kg for both sexes. A 10% dermal absorption factor is recommended for all dermal exposure scenarios, based on the previous 2006 risk assessment (C. Smith, D328478, 06/28/2006).

4.3 Toxicological Effects

The most common effect in animal studies from intermediate- or long-term oral exposure was a decrease in body weight or body weight gain. Rats were more sensitive than mice, and in both species, females were more sensitive than males to effects on body weight. In chronic studies, the basis for the lowest observed adverse effect levels (LOAELs) was a decrease in body weight and body weight gain by female rats (1.88 mg/kg/day) and male and female mice (111 and 124 mg/kg/day, respectively). The no observed adverse effect level (NOAEL) for chronic toxicity in rats was 0.375 mg/kg/day but a NOAEL was not identified in mice.

Decreased maternal body weight gain was also observed in developmental toxicity studies with rats and mice (1.5 and 24 mg/kg/day, respectively). Additionally, rats showed clinical signs of toxicity (salivation and rubbing the face and paws after treatment) at maternal doses as low as 0.75 mg/kg/day. Developmental toxicity was observed as decreased fetal body weight (23%) in rats (maternal 6 mg/kg/day) and increased resorptions (3.8 vs. 0.5 controls) with correspondingly fewer live fetuses/litter in mice (8.2 vs. 10.8 controls, maternal 24 mg/kg/day). No treatment-related structural external, visceral, or skeletal abnormalities were found in fetuses from treated dams.

In a two-generation reproductive toxicity study (rat) with rotenone, adult and offspring toxicity were observed at doses greater than 3.0 mg/kg/day. The main effect in both parental animals and pups was decreased body weight and body weight gain. Females were more sensitive than males and the magnitude of effects was similar between generations. Parental toxicity was indicated by decreased absolute body weight and body weight gain for the high-dose males and females (4.8 and 6.2 mg/kg/day, respectively) and the mid-dose females (3.0 mg/kg/day) of both generations. Food consumption was only marginally affected and mainly in the high-dose groups. Decreased maternal weight gain by the 6.2-mg/kg/day F_0 and F_1 dams during gestation correlated with a

decrease in the mean number of live pups/litter in the high-dose groups of both generations (9.7-9.9 vs. 11.4-11.8 for the controls). F_1 and F_2 offspring body weight was slightly or significantly less than that of controls for the 6.2-mg/kg/day pups beginning at birth and for the 3.0-mg/kg/day pups beginning on post-natal day (PND) 4. Body weight gain was reduced in the mid- (20-26%) and high-dose (40-60%) pups of both generations throughout lactation beginning with the interval PND 0-4.

None of the results from the available studies, except the acute oral toxicity study (tremors, prostration, labored breathing, and soft feces), showed evidence of neurotoxicity. In a special non-guideline continuous intravenous study (Betarbet *et al.,* 2000, MRID# 45279501) with Lewis rats, exposure to rotenone (2.5-2.75 mg/kg/day) produced behavioral, biochemical, and neuropathological effects that resemble Parkinson's disease in humans. Intravenous rotenone induced specific neurodegenerative lesions in nigrostriatal dopaminergic neurons; however, no oral studies resulted in dopaminergic effects. Clinical signs in affected animals included hypoactivity, unsteady gait, and hunched posture. There is no information regarding the inhalation toxicokinetics of rotenone to better compare the intravenous and inhalation routes. The only available inhalation toxicity study is an acute LC_{50} study in the rat. Therefore, a DCI (Data Call In) was issued (DCI GDCI-071003-20980**,** 02/09/2004, D307369) requesting a 21-day inhalation neurotoxicity study in the Lewis rat. No study has been submitted and a submitted data waiver request was denied (Locke, 2004).

Rotenone is classified as Group E - evidence of non-carcinogenicity for humans (R. Gardner, TXR 0052673, 10/05/1988). No evidence for carcinogenicity was seen in mice or rats from available carcinogenicity studies. Administration of rotenone to both species for up to two years did not result in an increase in overall tumor incidence or increase the incidence of any specific type of tumor. The chemical was negative for gene mutation in two studies with *Salmonella typhimurium* and for mitotic gene conversion with *Saccharomyces cerevisiae*. Micronucleus formation was not induced in the bone marrow of mice. Rotenone also did not cause chromosomal aberrations in CHO cells *in vitro* with or without activation or in bone marrow cells from rats administered up to 7 mg/kg orally. However, both the rat and mouse micronucleus and bone marrow assays are classified unacceptable/non-guideline since a maximum tolerated dose (MTD) was not achieved in either the rat or the mouse assays. Positive results for gene mutation were obtained only in mouse lymphoma cells, without metabolic activation, at concentrations equal to and below those which also caused significant cytotoxicity.

Rotenone is acutely toxic via the oral and inhalation routes of exposure (Toxicity Category I), with females more sensitive than males to acute oral toxicity. Rotenone was neither corrosive nor irritating to the skin or eye (Toxicity Category IV) and is not a dermal sensitizer.

4.3.1 Epidemiology Review Summary

HED conducted a Tier II Epidemiology review that included a systematic literature search of epidemiologic studies that examined the health effects associated with rotenone exposure (A. Niman, S. Recore, E. Evans, D456891, 03/19/2020). Based on this search, HED identified nine relevant articles, including eight articles on Parkinson's Disease (PD) and one article on Non-

Hodgkin's Lymphoma (NHL), that were evaluated using OPP's framework for incorporating epidemiological data into risk assessment.[5]

For the outcome PD, there was insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between rotenone exposure and PD. While some studies reported evidence of a positive association, notably the AHS-FAME study by *Tanner et al.* (2011),[6] the overall evidence was considered insufficient because the body of literature consisted of studies on five study populations that had relatively small sample sizes and substantive methodological limitations that make it difficult to rule out the role of chance, bias, and confounding with confidence. The AHS-FAME study by Tanner *et al*. (2011), for example, reported a strong association when evaluating ever/never exposure, but a dose-response trend was not apparent when the investigators stratified their analysis by median lifetime days of rotenone use (14 days). In fact, higher exposures (>median) showed reduced odds ratios compared to lower exposures (< median). In addition, the AHS-FAME studies were considered high quality, but still had important limitations that make it difficult to rule out bias and confounding with confidence. The evidence from the remaining four study populations was mixed and included one moderate quality case-control study reporting no association,[7] one moderate quality study that had an insufficient number of rotenone exposed cases,[8] one low quality case-control study that reporting conflicting evidence based on different measures of rotenone exposure that vary in specificity,[9] and one low quality cross-sectional study reporting no evidence of a significant association and no evidence of a dose-response.[10]

For the outcome NHL, there was no epidemiological evidence to conclude that there is a clear associative or causal relationship between the rotenone exposure and NHL. The association was examined in only a single study by De Roos et al. (2003) that performed a pooled analysis of three existing case-control studies that were conducted in Iowa, Nebraska, Kansas, and Minnesota.[11] The study was rated moderate and reported no evidence of an association, based on OR effect estimates that were less than one and had relatively wide confidence intervals.

Overall there was insufficient evidence to suggest a clear associative or causal relationship exists between rotenone exposure and any health effects observed in human populations evaluated by

[5] US EPA. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf. December 28, 2016.

[6] Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korel M, et al. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect. 2011, 119:866–872.

[7] Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein JM, et al. Editor's highlight: Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol Sci 2017;158(1):188-198.

[8] Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. Arch Neurol. 2009 Sep; 66(9): 1106-13.

[9] Dhillon AS, Tarbutton GL, JL Levin, MD, Plotkin GM, Lowry LK, Nalbone JT, Shepherd S. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromedicine. 2008, 13(1):37-48.

[10] Pouchieu C, Piel C, Carles C, Gruber A, Helmer C, Tual S, et al. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. Int J Epidemiol 2018;47(1):299-310.

[11] De Roos AJ, Zahm S, Cantor K, Weisenburger D, Holmes F, Burmeister L, and Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med.* 2003, 60(9).

HED. HED will continue to monitor the incident epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

4.4 Considerations for Infants and Children

Food Quality Protection Act (FQPA) considerations do not apply to rotenone for the currently registered (non-food) use patterns described in this risk assessment. The assessments are based on reliable exposure data and will not underestimate exposure. No increased offspring sensitivity over parent was observed in the available rat or mouse pre-natal developmental studies or the post-natal reproduction study. However, there is no developmental toxicity study available in a non-rodent species.

Due to data gaps in the toxicology database, an additional 10X UF has been applied to the various points of departure (PODs) selected.

4.4.1 Completeness of the Toxicology Database

The toxicity database for rotenone is incomplete; however, data are adequate for evaluation of effects resulting from *in utero* and post-natal exposure in rodents only. Two acceptable developmental toxicity studies have been conducted in rodents (mice and rats) and a reproductive toxicity study in rodents (rats) is available. It is noted that a developmental toxicity study in nonrodents (rabbit) has not been submitted and is required for rotenone if occupational exposure is significant. HED notes that rotenone is applied by highly-trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water). In the available studies, developmental toxicity was observed in both rats and mice at doses greater than or equal to those resulting in maternal toxicity. At the same dose that resulted in adult toxicity, offspring growth was decreased during the first four days of lactation, prior to direct contact with rotenone by the pups.

4.4.2 Evidence of Neurotoxicity

In acute lethality studies, clinical signs included tremors, prostration, labored breathing, and soft feces following oral dosing and decreased activity, gasping, piloerection, ptosis, and sensitivity to touch after inhalation exposure. No clinical signs of toxicity were noted in subchronic or chronic studies in dogs, rats, mice, or hamsters. Histopathology of the nervous system is not typically evaluated in these subchronic or chronic studies.

No acute or subchronic neurotoxicity studies are available for rotenone. In a special non-guideline study with rats, continuous intravenous exposure for up to 5 weeks produced behavioral, biochemical, and neuropathological effects that resemble Parkinson's disease; however, no oral studies resulted in dopaminergic effects. Except for one LC50 study, no inhalation studies have been conducted.

Based on a WOE approach, considering all the available hazard and exposure data for rotenone, the HASPOC recommended that if exposure is determined to be significant, the subchronic inhalation study with neurotoxicity parameters and the developmental toxicity study (rabbit) remain required studies at this time. The HASPOC recommended that the acute and subchronic neurotoxicity studies, immunotoxicity study, and subchronic (90-day) dermal study for rotenone be waived. HED notes that rotenone is applied by highly-trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water).

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No quantitative or qualitative evidence supports increased susceptibility of rat or mouse fetuses or rat offspring. Fetuses were affected from *in utero* exposure to rotenone in the developmental toxicity studies at the same dose that resulted in maternal toxicity. Likewise, post-natal growth and survival were reduced prior to direct exposure to the test material at the same or higher doses, respectively, that caused adult systemic toxicity. In rats, the same endpoint of toxicity, reduced body weight, was the main effect in adults, fetuses, and offspring.

A non-rodent developmental toxicity is currently unavailable. It is possible that toxicity not observed in the available rodent developmental toxicity studies would be identified in the non-rodent developmental toxicity study. However, in available rat studies, developmental and offspring toxicity occurred at doses that also caused parental/adult toxicity; qualitatively the effect in all ages was the same, *i.e.*, reduced body weight and weight gain. For the relevant studies in rats, well defined NOAELs were identified as 3 and 0.6 mg/kg/day for developmental and offspring effects, respectively.

4.4.4 Residual Uncertainty in the Exposure Database

The acute, subchronic, and chronic toxicity of rotenone is well understood for the currently identified exposure pathways. The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. There are no residual uncertainties in the exposure database based on: (1) the registered use is a non-food use, and (2) adequate exposure data are available to assess residential exposure resulting from the registered uses.

4.5 Toxicity Endpoint and Point of Departure Selections

Toxicity studies used to select PODs for each exposure scenario are presented in Appendix A.2. PODs were selected for dietary (acute and chronic), incidental and adult oral, dermal (short- and intermediate-term), and inhalation (short- and intermediate-term) scenarios. The PODs, uncertainty factors, and calculated reference dose (RfD)/population adjusted dose (PAD) or level of concern (LOC) for each exposure scenario are detailed in Table 4.5.3.1. The PODs have not changed since the last risk assessment in 2006 (C. Smith, D328478, 06/28/2006).

Acute Dietary (Females 13-49 years old):
The developmental toxicity in mouse (MRID 00141407) was selected with a NOAEL of 15 mg/kg/day and a LOAEL of 24 mg/kg/day based on increased resorptions. The Uncertainty Factor (UF) is 1000; includes 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 10X for database uncertainty. At the LOAEL, increased resorptions resulted in fewer numbers of live fetuses/litter. This effect could have resulted from one or two exposures during development. Therefore, this developmental effect has implications for women of childbearing age. Since the effect occurred during development from one or two exposures, the duration is appropriate for this scenario. Application of a 10X UF_{db} is recommended based on the lack of several studies.

Acute Dietary (General Population):
A dose and endpoint are not proposed because, based on the available data, a single dose endpoint was not identified for the general population, including infants and children.

Chronic Dietary:
The chronic/oncogenicity study in rats (MRID 00156739 and 41657101) was selected with a NOAEL of 0.375 mg/kg/day and a LOAEL of 1.88 mg/kg/day based on decreased body weight and food consumptions in females. The Uncertainty Factor (UF) is 1000; includes 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 10X for database uncertainty. The duration of dosing and the endpoint are appropriate for this scenario. Application of the UF_{db} is required due to the lack of several studies.

Incidental and Adult Oral Exposure (Short- and Intermediate-term):
The reproductive toxicity study in rats (MRID 00141408) was selected with the parental and offspring toxicity NOAEL of 0.5 mg/kg/day based on decreased body weight and body weight gain at 2.4 and 3.0 mg/kg/day for males and females, respectively. The Uncertainty Factor (UF) is 1000; includes 10x for interspecies extrapolation, 10X for intraspecies extrapolation, and 10X for database uncertainty. Reductions in offspring body weight began as early as PND 4 indicating that the effect began before the pups had direct contact with the food.

Dermal (Short-, Intermediate- and Long-term):
The reproductive toxicity study in rats (MRID 00141408) is selected with the parental toxicity NOAEL of 0.5 mg/kg/day based on decreased body weight and body weight gain at 2.4 and 3.0 mg/kg/day in males and females, respectively. The Uncertainty Factor (UF) is 1000; includes 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 10X for database uncertainty. A 10% dermal absorption factor is recommended for all dermal exposure scenarios.

Inhalation Exposure (Short- and Intermediate-term):
A reproductive toxicity study in rats (MRID# 00141408) was selected with the parental toxicity NOAEL of 0.5 mg/kg/day and a LOAEL of 2.4 and 3.0 mg/kg/day (M/F) based on decreased body weight and body weight gain. The Uncertainty Factor (UF) is 1000; includes 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 10X for database uncertainty.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

The dermal, inhalation, and incidental oral exposures can be combined because the endpoints are based on the same toxicological effects.

4.5.2 Cancer Classification and Risk Assessment Recommendation

No evidence for carcinogenicity was seen in mice or rats and it is not mutagenic *in vitro* or *in vivo*. Therefore, rotenone is classified as Group E (evidence of non-carcinogenicity for humans) (Memo, R. Gardner, TXR 0052673, 10/05/1988).

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3: Summary of Toxicological Points of Departure and Endpoints for Rotenone for Use in Human Health Risk Assessments

Exposure/ Scenario	Point of Departure POD	Uncertainty Factors/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49)	NOAEL = 15 mg/kg	UF_A=10x UF_H=10x UF_{DB}=10x	aRfD = aPAD = 0.015 mg/kg/day	Developmental Toxicity – mouse MRID 00141407 LOAEL = 24 mg/kg/day, based on increased resorptions
Acute Dietary (General Population including infants and children)	An appropriate endpoint attributable to a single dose was not identified in the available studies, including the developmental toxicity studies			
Chronic Dietary	NOAEL = 0.375 mg/kg/day	UF_A=10X UF_H=10X UF_{DB}=10X	cRfD = cPAD = 0.0004 mg/kg/day	Chronic/Carcinogenicity (rat) Feeding Toxicity MRID 41657101 LOAEL = 1.88 mg/kg/day, based on decreased body weight and food consumption in both sexes
Incidental/Adult Oral and Short- and Intermediate-Term	NOAEL = 0.5 mg/kg/day	UF_A=10X UF_H=10X UF_{DB}=10X	Residential LOC = 1000	Reproductive Toxicity Study in Rats MRID 00141408 LOAEL = 2.4/3.0 mg/kg/day (M/F), based on decreased parental and offspring (M&F) body weight and body weight gain
Dermal All Durations	Oral NOAEL = 0.5 mg/kg/day (Dermal Absorption factor = 10%)	UF_A=10X UF_H=10X UF_{DB}=10X	Residential/ Occupational LOC = 1000	Reproductive Toxicity Study in Rats MRID 00141408 LOAEL = 2.4/3.0 mg/kg/day (M/F), based on decreased parental (M&F) body weight and body weight gain

Table 4.5.3: Summary of Toxicological Points of Departure and Endpoints for Rotenone for Use in Human Health Risk Assessments				
Inhalation Short- and Intermediate-Term	Oral NOAEL = 0.5 mg/kg/day 100% inhalation absorption factor	UF_A=10X UF_H=10X UF_{DB}=10X	Residential/ Occupational LOC = 1000	Reproductive Toxicity Study in Rats MRID 00141408 LOAEL = 2.4/3.0 mg/kg/day (M/F), based on decreased parental (M&F) body weight and body weight gain
Cancer (oral, dermal, inhalation)	**Classification:** Group E (evidence of non-carcinogenicity for humans)			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. RfD = reference dose (a = acute; c= chronic). UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_D = uncertainty in the database because of missing studies. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

4.6 Endocrine Disruptor Screening Program

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for rotenone, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), rotenone is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list

of chemicals identified for EDSP screening was published on June 14, 2013[12] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

No acceptable metabolism studies or analytical method are available to support the nature of the residue guideline requirements. Metabolism studies and an analytical method are no longer required because there are currently no registered or proposed uses of rotenone on any food or feed item.

5.2 Food Residue Profile

There are no currently registered food uses for rotenone; therefore, residue chemistry data are not required for rotenone at this time.

5.3 Water Residue Profile

HED has completed dietary exposure and risk assessment using an EDWC of 40 µg/L based on the rotenone SOP Manual and no new drinking water estimates were needed for this assessment. Based on the SOP Manual language, although applications of rotenone may occur at higher rates, users are advised to not consume treated water until residues are <40 ppb. The rotenone SOP provides specific guidance on the monitoring requirements and analysis of water samples for rotenone-treated drinking water. When rotenone applications occur in waters with drinking water intakes or with hydrologic connections to wells, 7 to 14 days prior to application, the Certified Applicator or designee under his/her direct supervision must provide notification to the party responsible for the public water supply or to individual private water users against the consumption of treated water until one of the following conditions are met: 1) rotenone levels are below 40 ppb as determined by analytical chemistry, or 2) fish samples (Salmonidae or Centrarchidae) families can survive up to 24 hours, or 3) dilution with untreated water results in a rotenone concentration <40 ppb, or 4) distance or travel time from the application sites demonstrate that active rotenone is <40 ppb.

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[12] Melamed E., Rosenthal J., and Youdim M.B.H. 1990. Immunity of fetal mice to prenatal administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. J. Neurochem. 55: 1427-1431.
[12] Eriksson P., Johansson U., Ahlbom J., and Fredriksson A 1993. Neonatal exposure to DDT induces increased susceptibility to pyrethroid (bioallethrin) exposure at adult age- Changes in cholinergic muscarinic receptor and behavioral variables. Toxicology. 77:21-30.
[12] Eriksson P. 1996. Developmental neurotoxicology in the neonate- Effects of pesticides and polychlorinated substances. Arch. Toxicol. Suppl. 18: 81-88.
[12] Gupta a., Agarwal R., and Shukla G.S., 1993. Functional impairment of the blood-brain barrier following pesticide exposure during early development in rats. Hum. Exp. Toxicol. 18: 174-179.
[12] Thiruchelvam M., Richfield E.K., Goodman B.M., Baggs R.B., and Cory-Slechta D.A., 2002. Developmental exposure to pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotox. 33: 621-633.
[12] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

Previously EFED conducted a drinking water assessment for rotenone in 2005 in which the most conservative acute concentrations were considered to be the maximum treatment concentrations of 250 µg/L and 50 µg/L for lakes and rivers, respectively. These values, which are target treatment concentrations and not results from modeling, would decrease as the treatment concentrations for rotenone have changed. The EDWC recommended by EFED for the acute dietary exposure and risk assessment is 200 µg/L (which is solubility limit at 20 C and the current target concentration on the majority of the labels and SOP). EFED has not recommended an EDWC for chronic dietary exposure and risk assessment purposes since rotenone degrades in water and may be deactivated through the use of a strong oxidizing agent (typically potassium permanganate) before it leaves the targeted treatment site; therefore, chronic exposure is not expected (email communication with EFED 12/11/2019).

Two acute assessments were conducted using the acute EDWCs of 40 µg/L and 200 µg/L. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." HED notes that rotenone degrades relatively rapidly in aquatic systems ($t_{1/2}$ ca. 1-30 days;) and that the maximum concentration would not remain for an extended period of time following treatment.

The maximum application rate for the piscicidal use of rotenone (250 ppb) on one label (EPA Reg. No. 19713-316) exceeds the solubility of rotenone in water. However, as mentioned above, that the maximum application rate stated in the SOP Manual and majority of the labels is 200 ppb and does not exceed the limit of solubility in drinking water. Therefore, it is unlikely the rotenone treatment concentration in water exceeds 200 ppb and HED's characterization assessment is conservative.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Acute dietary (fish + drinking water) exposure and risk assessments were conducted for rotenone, using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

Rotenone is registered only for piscicidal uses, with restrictions to prevent consumption of treated fish. Based on the use pattern and restrictions (Section 5.3), long-term consumption of fish or drinking water bearing residues of rotenone is extremely unlikely. Therefore, HED has determined that a quantitative chronic dietary exposure assessment is not necessary. Although acute consumption of rotenone residues in fish is also unlikely, HED has conducted a highly conservative acute dietary exposure assessments to address the scenario where fish survive the treatment process and are consumed. The assessments also included an estimated drinking water concentration (EDWC) of 40 µg/L based on rotenone SOP Manual. For purposes of characterization, HED also included an EDWC of 200 µg/L, which is the limit of solubility and maximum application rate for the majority of labels and SOP.

HED has conducted two acute dietary exposure and risk assessments for females 13-49 years of age assuming EDWCs of 40 ppb and 200 ppb and a theoretical point estimate for freshwater finfish (wild and farm-raised). However, there is no tolerance for rotenone residues in fish. The USDA Pesticide Data Program (PDP) monitored rotenone residues in catfish in 2008. In this period, PDP analyzed 552 samples of catfish. None of the samples contained detectable residues. PDP did not analyze catfish samples for residues of rotenone in 2009 and 2010. HED notes that although rotenone is a piscicide, detectable residues in PDP are not expected for catfish. Catfish in this context are not considered to be a nuisance fish and, therefore, would not be expected to receive rotenone treatment. The calculated theoretical maximum residues in fish based on a bluegill bioaccumulation study (W. H. Gingerich and J. J. Rach, MRID 00146183, 06/18/1985) were included in this assessment and are protective of any potential exposures. Therefore, the HED dietary exposure and risk assessment is conservative and protective for risks from potential dietary exposures.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Not applicable.

5.4.3 Acute Dietary Risk Assessment

Acute dietary exposure assessments were performed for females 13-49 years of age, the only population subgroup for which an acute dietary endpoint was identified. The assessments considered exposures from drinking water and fish only.

The resulting acute dietary risk estimate (fish + water) using the EDWC of 40 µg/L was 17% of the aPAD at the 95th percentile of exposure and is below HED's level of concern (<100 % aPAD). With the EDWC of 200 µg/L, the risk estimate is 84% aPAD and remains below HED's level of concern. The results are summarized in Table 5.4.6.1 below.

An acute dietary assessment was also conducted for exposure from drinking water only since drinking water was the main driver. The dietary risk estimates (drinking water only) for females 13-49 years old using 40 µg/L was 15% of the aPAD at the 95th percentile of exposure and is below HED's level of concern (<100 % aPAD). With EDWC of 200 µg/L, the risk estimate was 73% of the aPAD and remains below HED's level of concern. The results are summarized in Table 5.4.6.2 below.

5.4.4 Chronic Dietary Risk Assessment

Long term exposure for rotenone in water is not expected based on the use pattern and restrictions. Fish treated with rotenone are not for consumption. The rotenone use pattern indicates that fish in the rotenone treated area should be collected and buried. Restocking of fish or drinking water after rotenone treatment requires the collection and analysis of water samples to verify the rotenone is non-detectable prior to restocking of the treated water with fish and/or fish can survive for 24 hours. In addition, in flowing water system rotenone may be deactivated using potassium permanganate before it is released to the flowing system. Rotenone also

degrades at least moderately rapidly in aquatic environments; thus, it is unlikely that residues will accumulate and persist for long period in water or sediment.

Based on the use pattern and restrictions noted above, long-term consumption of fish or drinking water bearing residues of rotenone is extremely unlikely; therefore, a chronic dietary exposure and risk assessment has not been conducted.

5.4.5 Cancer Dietary Risk Assessment

There is no evidence of carcinogenicity associated with rotenone; therefore, a cancer dietary assessment was not performed.

5.4.6 Summary Table

Table 5.4.6.1 Summary of Dietary (Fish and Drinking Water) Exposure and Risk for Rotenone

Population Subgroup	Acute Dietary				
	aPAD (mg/kg/day)	EDWC= 200 ppb (µg/L)		EDWC= 40 ppb (µg/L)	
		Dietary Exposure, 95th percentile (mg/kg/day)	% aPAD	Dietary Exposure, 95th percentile (mg/kg/day)	% aPAD
Females 13-49 years old	0.015	0.012658	84	0.002558	17

Table 5.4.6.2. Summary of Dietary (Drinking Water Only) Exposure and Risk for Rotenone

Population Subgroup	Acute Dietary				
	aPAD (mg/kg/day)	EDWC= 200 ppb (µg/L)		EDWC= 40 ppb (µg/L)	
		Dietary Exposure, 95th percentile (mg/kg/day)	% aPAD	Dietary Exposure, 95th percentile (mg/kg/day)	% aPAD
Females 13-49 years old	0.015	0.010884	73	0.002177	15

6.0 Residential Exposure/Risk Characterization

6.1 Residential Handler Exposure/Risk Estimates

There are no registered or proposed uses for residential handlers at this time for rotenone. A residential handler assessment was not completed.

6.2 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with rotenone. The updated quantitative short-term exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Residential adults: inhalation, dermal, and oral ingestion by individuals of the general population from engaging in swimming activities in water previously treated with

rotenone.

- Residential children (3 to < 6 years old): inhalation, dermal, and oral ingestion by individuals of the general population from engaging in swimming activities in water previously treated with rotenone.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[13] and the 2015 draft Aquatic Use SOP. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor are detailed in the 2012 Residential SOPs[13] and the 2015 draft Aquatic Use SOP.

Combining Exposure and Risk Estimates

Since dermal, inhalation, and oral ingestion exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. Therefore, the post-application exposure scenarios that were combined for adults and children 3 < 6 years old are the dermal, inhalation, and oral ingestion scenarios. This combination should be considered a protective estimate of children's exposure from swimming in rotenone treated waters.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

Residential post-application exposure can occur from swimming in previously treated waters with residual rotenone. Based on the Rotenone SOP, public waters will be marked with signs prohibiting entering and swimming until the rotenone levels in the water are determined to be at safe levels (< 90 ppb, as noted by the SOP Manual) by a licensed handler. Nevertheless, residential post-application exposure was assessed to determine the potential risks posed to adults and children, both immediately after rotenone application and once rotenone concentrations are <90 ppb. Residential post-application combined (dermal, inhalation, and oral) MOEs for the registered uses range from 14,400 to 17,700 (LOC = 1,000) for adults and 2,100 to 2,500 (LOC = 1,000) for children with rotenone concentrations in water equal to the application rate. Residential post-application combined MOEs for the registered uses after concentration has reached below the restricted concentration of rotenone in water (<90 ppb) are 5,800 (children 3<6 years old) and 41,000 (adults) (LOC = 1,000). All MOEs are above the LOC and therefore no residential post-application risk estimates are of concern.

[13] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.2.1. Short-term Residential Post-application Non-cancer Exposure and Risk Estimates for Rotenone.

Use Site	Post-application Exposure Scenario		Application Rate[1]	Chemical Concentration in Water[1] (CW)	Dose (mg/kg/day)[2]	MOEs[3] (LOC= 1,000)	Combined MOEs[4] (LOC= 1,000)
	Lifestage	Route of Exposure					
Flowing water	Adult	Inhalation	0.54 lb ai/acre-ft or 0.000013 lb ai/ft^3	0.209 mg/L (209 ppb)	7.8E-13	640,000,000,000	17,700
		Dermal			1.5E-05	33,000	
		Oral Ingestion			1.3E-05	38,000	
	Child (3 to <6 years old)	Inhalation			5.4E-12	93,000,000,000	2,500
		Dermal			0.00006	8,000	
		Oral Ingestion			0.00014	3,600	
Non-Flowing water	Adult	Inhalation	0.68 lb ai/acre-ft or 0.000016 lb ai/ft^3	0.257 mg/L (257 ppb)	9.6E-13	520,000,000,000	14,400
		Dermal			0.0015	27,000	
		Oral Ingestion			1.6E-05	31,000	
	Child (3 to <6 years old)	Inhalation			6.63E-12	75,000,000,000	2,100
		Dermal			0.0015	6,500	
		Oral Ingestion			0.00017	3,000	
Restricted Concentration (< 90 ppb) Flowing and non-flowing water	Adult	Inhalation	Determined safe levels (< 90 ppb) by a licensed handler	0.090 mg/L (90 ppb)	3.4E-13	1,500,000,000,000	41,000
		Dermal			6.5E-06	76 ,000	
		Oral Ingestion			5.6E-06	89, 000	
	Child (3 to <6 years old)	Inhalation			2.3E-12	220,000,000,000	5,800
		Dermal			0.00003	19 ,000	
		Oral Ingestion			5.9E-05	8,400	

1 Based on maximum application rate for all registered labels, see Section 3.3.
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) and draft Aquatic SOP.
3 MOE = POD (0.5 mg/kg/day) ÷ Dose (mg/kg/day).
4 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/inhalation MOE) + (1/incidental oral MOE)], where applicable.

6.3 Residential Risk Estimates for Use in the Combined Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the combined assessment for rotenone:

- The recommended residential exposures for use in the adult combined assessment are dermal, inhalation, and oral ingestion exposures from post-application exposure to treated water at the restricted concentration (<90 ppb water).
- The recommended residential exposure for use in the children 3<6 years old combined assessment are dermal, inhalation, and oral ingestion exposures from post-application exposure to treated water at the restricted concentration (<90 ppb water).

Table 6.3.1. Recommendations for the Residential Exposures for the Rotenone Combined Assessment.

Lifestage	Dose (mg/kg/day)[1]				MOE[2]			
	Dermal	Inhalation	Oral Ingestion	Total	Dermal	Inhalation	Oral Ingestion	Total
Adult (<90 ppb)	6.5E-06	3.4E-13	5.6E-06	**1.21E-05**	76,000	1,500,000,000,000	89,000	**41,000**
Child (<90 ppb)	0.00003	2.3E-12	5.9E-05	**8.90E-05**	19,000	220,000,000,000	8,400	**5,800**

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

7.0 Combined Exposure/Risk Characterization

Food Quality Protection Act (FQPA) considerations do not apply to rotenone for the currently registered (non-food) use patterns described in this risk assessment; however, HED did consider a combined assessment to account for potential exposures from residential and dietary exposures. In a combined assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be combined. When combining exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Combined Risk

The acute combined assessment is equivalent to the acute dietary assessment. The acute dietary exposure estimates (fish + water) are below HED's level of concern at the 95th percentile of exposure (<100 % aPAD).

7.2 Short-Term Combined Risk

Based on the use pattern and label restrictions, chronic dietary exposure to rotenone is not anticipated; therefore, the short-term combined assessment is equivalent to the residential post-application exposure assessment and is not of concern.

7.3 Chronic Combined Risk

Rotenone is registered only for piscicidal uses, with restrictions to prevent consumption of treated fish. Based on the use pattern and restrictions (Section 5.3), long-term consumption of fish or drinking water bearing residues of rotenone is extremely unlikely. Therefore, HED has determined that a quantitative chronic dietary exposure assessment is not necessary, and thus chronic combined assessment, is not necessary.

7.4 Cancer Aggregate (Combined) Risk

There is no evidence of carcinogenicity associated with rotenone; therefore, a cancer combined assessment was not performed.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[14] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of rotenone. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[15,16] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (*i.e.,* the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (*e.g.,* herbicides are not typically applied to tree canopies) or specific label prohibitions (*e.g.,* aerial applications are not allowed). Section 6.1 provides the screening level drift related risk estimates.

In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

[14] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[15] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift

8.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Rotenone is used on flowing and non-flowing water to manage fish populations and can be applied via aerial equipment. The recommended drift scenario screening level options are listed below:

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[17]

    - The application rate for the aerial application was modified slightly to account for the amount of ai applied per area-depth. The highest application rate for aerial applications of rotenone is 0.68 lbs ai/acre-foot with an assumed depth of 7 feet. Therefore, the application rate for the spray drift assessment is 0.68 lbs ai/acre-foot × 7 feet = 4.76 lbs ai/acre.
    - HED notes that aerial applications were intended to be removed from labels, therefore, this scenario may be limited. Also, given the target of rotenone as a piscicide is to achieve subsurface concentration for efficacious fish kill, smaller droplets are unlikely to be a preferred application method and more targeted applications are likely utilized.

Spray drift estimates for aerial applications of rotenone are of concern. The MOEs for the spray drift assessment range from 3 to 20 (LOC = 1,000) for children 1 < 2 years old and adults at the edge of the treated area and continue to be of concern (MOEs < LOC of 1000) 300 feet from the treated area.

[17] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

Table 8.1.1 Spray Drift Risk Estimates for Aerial Applications to Aquatic Areas with Rotenone														
Rate Group	**Spray Type/ Nozzle Configuration**	**Application Rate (lb ai/A)[1]**	**Estimated TTR (ug/cm2)**	**At Edge**	**10ft**	**25ft**	**50ft**	**75ft**	**100ft**	**125ft**	**150ft**	**200ft**	**250ft**	**300ft**
				MOE (LOC = 1,000)										
Adult (Dermal)														
Aerial	***Fine to Medium***	4.76	0.529074	11	13	17	22	29	37	44	52	68	82	100
	Medium to Coarse			13	18	24	34	48	64	80	97	130	180	220
	Coarse to Very Coarse			15	23	34	53	76	100	130	160	220	280	350
	Very Fine to Fine			8	8	9	11	12	14	16	18	22	26	29
	AT401, M, 10 mph, 37% SD			12	15	20	27	36	47	57	67	88	110	130
	WASP, M, 10 mph, 37% SD			13	16	22	33	44	57	70	82	110	130	160
	AT401, C, 10 mph, 25% SD			14	20	28	42	60	78	97	120	160	220	250
	WASP, C, 10 mph, 25% SD			16	23	33	53	74	100	120	160	220	280	310
	AT401, VC, 10 mph, 20% SD			16	24	39	64	90	120	160	200	280	350	470
	WASP, VC, 10 mph, 20% SD			20	32	49	78	110	150	200	230	350	400	470
Children 1<2 years old (Combined, Dermal and Hand to Mouth)														
Aerial	**Fine to Medium**	4.76	0.529074	5	6	7	9	12	15	19	22	29	35	42
	Medium to Coarse			6	8	10	14	20	27	34	40	56	73	90
	Coarse to Very Coarse			6	10	14	22	32	42	53	65	90	120	150
	Very Fine to Fine			3	4	4	5	5	6	7	8	9	11	12
	AT401, M, 10 mph, 37% SD			5	6	8	11	15	20	24	28	37	45	56
	WASP, M, 10 mph, 37% SD			5	7	9	14	19	24	29	35	45	56	65

Table 8.1.1 Spray Drift Risk Estimates for Aerial Applications to Aquatic Areas with Rotenone														
Rate Group	**Spray Type/ Nozzle Configuration**	**Application Rate (lb ai/A)[1]**	**Estimated TTR (ug/cm2)**	**At Edge**	**10ft**	**25ft**	**50ft**	**75ft**	**100ft**	**125ft**	**150ft**	**200ft**	**250ft**	**300ft**
				MOE (LOC = 1,000)										
	AT401, C, 10 mph, 25% SD			6	8	12	18	25	33	40	49	69	90	110
	WASP, C, 10 mph, 25% SD			7	10	14	22	31	42	51	65	90	120	130
	AT401, VC, 10 mph, 20% SD			7	10	16	27	38	51	65	84	120	150	200
	WASP, VC, 10 mph, 20% SD			9	13	21	33	47	62	84	98	150	170	200

[1] Application rate in lb ai/acre-foot (0.68 lbs ai/acre-foot) × Depth of water (7 feet from Aquatic SOP) = Application rate in lb ai/acre (4.76 lbs ai/acre)

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).
During Registration Review, the agency will utilize this analysis to determine if data (*i.e.*, flux studies, route-specific inhalation toxicological studies) or further analysis is required for rotenone.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to rotenone and any other substances and rotenone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that rotenone has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[18] and conducting cumulative risk assessments (CRA)[19]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for rotenone suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

[18] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)
[19] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

11.1 Short-/Intermediate-Term/ Occupational Handler and Post-application Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Short-term and intermediate-term exposure is expected for the occupational handlers for rotenone. Occupational handlers are expected to be exposed by dermal and inhalation routes of exposure. Piscicidal applications of rotenone are applied using several types of application equipment – including helicopters, closed system aspirators, boats with over-surface booms, boats with underwater hoses, drip bars (in rivers and streams), and backpack sprayers. Occupational handlers are required to wear coveralls, long-sleeved shirt, long pants, chemical resistant shoes plus socks, chemical-resistant gloves, and a dust/mist filtering respirator. Rotenone is a restricted use pesticide (RUP). It is unlikely for occupational workers to come into contact with previously treated water except for water sampling and dead fish collection. Tasks after an application require the same label-specified PPE as handlers if the rotenone application is >90 ppb, such as deactivating with potassium permanganate, handling dilute rotenone solutions (*i.e.*, testing rotenone-treated water), and other post-application tasks. HED does not have data to assess these activities, which are assumed to be negligible when compared to the occupational handler exposure scenarios. All occupational exposures are reflected by the handler assessment therefore a separate post-application assessment is not conducted.

HED notes that rotenone is applied by -trained applicators who are required to follow an SOP Manual with detailed instructions regarding the application and post-application procedures, all of which are anticipated to decrease the likelihood of applicator and post-application exposures (including drinking water). The SOP Manual can be found at https://units.fisheries.org/rotenone-stewardship/.

The occupational use patterns have not changed since the 2006 Final HED Chapter of the Reregistration Eligibility Decision Document (RED) (D328478). While individual inputs of unit exposures and amounts handled may have been updated, the toxicological database and points of departure have not changed, therefore the overall risk picture for rotenone RUP uses remains consistent. For this reason, the occupational handler assessment was not revised for the purposes of Registration Review. Based on the two previous assessments (D328478 and D421308), occupational risk estimates are driven by the dermal route of exposure and result in combined risk estimates less than the target level of concern of 1,000 (MOEs < LOC = 1,000) for many of the scenarios. This continues to be the risk conclusions for the registered uses of rotenone.

Re-entry Restriction

Rotenone has low toxicity for by the dermal route (Category IV) of exposure and is not considered a dermal irritant. Rotenone has an acute inhalation of Category I toxicity and acute

oral of Category I toxicity. Based on the Rotenone SOP, re-entry into aquatic areas after application is only allowed for certified handlers or when the concentration of rotenone in the water is <90 ppb. Dissipation to 90 ppb from 200 ppb takes approximately 2 days and from 250 ppb takes approximately 3 days. A re-entry restriction of 2-3 days was determined based on rotenone dissipation to 90 ppb within that time period. (C. Smith, D328776, 06/28/2006).

12.0 Incident Review

HED conducted a Tier II Incident review of incident report data available four monitoring programs included OPP's Incident Data System (IDS), National Pesticide Information Center (NPIC), National Institute of Occupational Safety and Health (NIOSH) SENSOR-Pesticides, and California Pesticide Illness Surveillance (PISP) (A. Niman, S. Recore, E. Evans, D456891, 03/19/2020). There were very few (n=9) rotenone reported to the databases reviewed. Most (n=7) of the incidents occurred following application of a rotenone product - both residential and occupational applications. The other incidents occurred following post-application exposure to rotenone. It should also be noted that many of the incidents involved insecticidal applications of rotenone, which have been cancelled by EPA and are no longer permitted for residential or agricultural use.

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report. These health effects primarily include respiratory, ocular, neurological gastrointestinal and dermal. HED did not identify any aberrant effects outside of those anticipated. These effects are generally mild/minor to moderate and resolve rapidly.
In addition to the databases queried, HED reviewed the document is entitled, "Accident Report Investigation: Reported Exposure to Rotenone by Illinois Water Science Center Employees During Asian Carp Rapid Response: December 2009 and May 2010." This document discussed two USGS employees who went out on a boat to monitor the rotenone's path through the waterways, a task which involved dye injection and measurements before the start of initial application and continued through the deactivation period eight hour after application. They both were diagnosed with Parkinson's disease a few years later. Both workers filed workers compensation claims in Illinois. Both claims were denied. IL WSC conducted an investigation of the accident. The IL WSC accident investigation report found that the two USGS employees' exposure to rotenone was "not significant" and the report concluded that "Adverse effects including neurological effects that result from exposure would not be expected."

After reviewing the IL WSC investigation report, EPA concludes that given the lack of any case exposure data as explained in the investigation report, and the lack of other important information including specific counts of workers conducting monitoring in total and not just the two incident cases, as well as the amount of time that has passed since then (more than a decade), EPA is not able to further assess the acute exposures for these two cases.

EPA notes that the currently-registered Prentox Prenfish Toxicant label (EPA Reg. No. 89459-23) states that on page six that "Only protected handlers may be in the area during application." Further, the label requires coveralls, chemical-resistant gloves and footwear, protective eyewear, and a respirator for all handlers. The IL WSC report notes that the USGS cases were not wearing any PPE while following the rotenone plume and conducting tasks, including measurements in

which “employees checked and retrieved instrumentation from treated water”. This task was conducted during the rotenone application (as well as post-application) “dye injection and measurements were conducted just before the start of initial rotenone application through the deactivation period.”

13.0 References

D456893, 20-MAR-2020, A. Habtemichael, Rotenone: Acute Aggregate Dietary and Drinking Water Exposure and Risk Assessment for Registration Review.

D456892, 20-MAR-2020, V. Kurker, Rotenone. Occupational and Residential Exposure Assessment for the Registration Review of Rotenone

D456891, 19-MAR-2020, A. Niman, S. Recore, E. Evans, Rotenone: Tier II Incident and Epidemiology Report.

TXR 0058000, 20-MAR-2020. J. Leonard, Hazard and Science Policy Council (HASPOC) Memo

D427108, 08-SEP-2015, T. Steeger et. al., Registration Review: Draft Problem Formulation for Environmental Fate, Ecological Risk, Endangered Species, and Human Health Drinking Water Exposure Assessment for Rotenone

D421308. 07-AUG-2014, M. Sahafeyan et al., Rotenone. Section 18 Emergency Use for the Presidio Lake

D328478, 28-JUN-2006, C. Smith et al., Rotenone: Final HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 071003. DP Barcode: D328478

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for non-food use for rotenone are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1.1: Test Required for Non-food Use Pesticides		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rat)	CR	yes[1]
870.3150	Oral Subchronic (dog)	CR	no
870.3200	21/28-Day Dermal (rat)	no	no
870.3250	90-Day Dermal	yes	no[2]
870.3465	28-Day Inhalation	CR	-
870.3700a	Developmental Toxicity (rat)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	no[2]
870.3800	Reproduction (rat)	yes	yes
870.4100a	Chronic Toxicity (rat)	CR	yes[1]
870.4100b	Chronic Toxicity (dog)	no	no
870.4200a	Carcinogenicity (rat)	CR	yes
870.4200b	Carcinogenicity (mouse)	CR	yes
870.4300	Chronic/Carcinogenicity (rat)	CR	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus	yes	yes
870.5450	Mutagenicity—Rodent dominant lethal assay	no	-
870.5500	Mutagenicity— Bacterial DNA Damage or Repair Test	no	-
870.5550	Mutagenicity—Unscheduled DNA Synthesis	no	-
870.6100a	Acute Delayed Neurotoxicity. (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	no[2]
870.6200b	90 Day Neurotoxicity Screening Battery (rat)	CR	no[2]
870.6300	Developmental Neurotoxicity (rat)	CR	-
870.7485	General Metabolism (rat)	CR	no
870.7600	Dermal Penetration, *in vivo* (male rat)	CR	no[3]
870.7800	Immunotoxicity (rat or mouse)	yes	no[2]

[1]Requirements for this study are fulfilled by the chronic/oncogenicity rat feeding study.

[2] J. Leonard, TXR 0058000, 03/20/2020. Memo Rotenone: Summary of Hazard and Science Policy Council (HASPOC) Meeting on February 20, 2020: Recommendations on the Need for a Subchronic Inhalation Neurotoxicity Study, Acute and Subchronic Neurotoxicity Studies, Developmental Toxicity Study (rabbit), 90-Day Dermal Study, and an Immunotoxicity Study.

[3]CFR 158.340 (24): Dermal absorption studies required for compounds having a serious toxic effect as identified by oral or inhalation studies, for which a significant route of human exposure is dermal and for which the assumption of 100 percent absorption does not produce an adequate margin of safety. Registrants should work closely with the Agency in developing an acceptable protocol and performing dermal absorption studies.

A.2 Toxicity Profiles

A 2.1 Acute Toxicity Profile: Rotenone				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat 99.23% a.i.	00145496 00147579	LD_{50} = 102 ± 12.6 mg/kg (M) LD_{50} = 39.5 ± 2.21 mg/kg (F)	I
870.1200	Acute dermal – rabbit 97.9% a.i.	43907501	$LD_{50} \geq 5000$ mg/kg (M & F)	IV
870.1300	Acute inhalation – rat 98% a.i.	43882601	LC_{50} = 0.0235 mg/L (M) LC_{50} = 0.0194 mg/L (F) LC_{50} = 0.0212 mg/L (C)	I
870.2400	Acute eye irritation – rabbit 97.9% a.i.	43907503	Minimal, in unwashed eyes conjunctival irritation, PIS 3.3 at 1 hour, cleared less than 24 hours	IV
870.2500	Acute dermal irritation – rabbit 97.9% a.i.	43907504	PIS 0.08 at 1 hour which decreased to 0 at 72 hours	IV
870.2600	Skin sensitization – guinea pig (Buehler) 98% a.i.	43817903	Not a dermal sensitizer	NA

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile of Rotenone[1]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100 82-1a 90-Day oral toxicity (rat)	Satisfied by MRID 00156739, 41657101 (83-5)	
870.3150 82-1b 90-Day oral toxicity (dog)	00141406 (1980) Acceptable/guideline M&F: 0, 0.4, 2, 10 mg/kg/day	**NOAEL** = 0.4 mg/kg/day **LOAEL** = 2 mg/kg/day based decreased body weight in mid-dose females (20%) and high-dose males and females (30%) and treatment-related inanition. (duration of treatment was 26 weeks)
870.3200 82-2 21/28-Day dermal toxicity	Not Available	
870.3250 82-3 90-Day dermal toxicity	Not Required	
870.3465 82-4 90-Day inhalation toxicity	Not Required. 21-Day study with neurological parameters is required (DCI GDCI-071003-20980; 02/09/2004).	
870.3700a 83-3a Developmental Toxicity (rat)	00144294 (1982) Acceptable/guideline F: 0, 0.75, 1.5, 3, 6 mg/kg/day (GD 6-19)	**Maternal NOAEL** = not identified **LOAEL** = 0.75 mg/kg/day, based on clinical signs of toxicity (salivation, rubbing of face and paws on cage in all groups). **Developmental NOAEL** = 3 mg/kg/day **LOAEL** = 6 mg/kg/day based on decreased fetal body weight (23%).

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile of Rotenone[1]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3700a 83-3a Developmental Toxicity (mouse)	00141407 (1981) (main) 00145049 (1981) (range-finding) Acceptable/guideline F: 0, 3, 9, 15, 24 mg/kg/day (GD 6-17)	**Maternal NOAEL** = 15 mg/kg/day **LOAEL** = 24 mg/kg/day, based on decreased body weight (10%) and body weight gain (41%), from range finding study. **Developmental NOAEL** = 15 mg/kg/day **LOAEL** = 24 mg/kg/day, based on increased resorptions (3.8 vs. 0.5 controls), from range-finding study. Acceptable when main and range-finding study considered together.
870.3700b 83-3b Developmental Toxicity (non-rodent/rabbit)	Not Available	
870.3800 83-4 Reproduction (rat)	00141408 (1983) Acceptable/guideline F0: M: 0, 0.5, 2.4, 4.8 mg/kg/d F0: F: 0, 0.6, 3.0, 6.2 mg/kg/day F1 (M):0, 0.6, 3.1, 7 mg/kg/day F1 (F): 0, 0.7, 3.7, 8.1 mg/kg/day	**Parental/Systemic NOAEL** (M/F) = 0.5/0.6 mg/kg/day **LOAEL** (M/F) = 2.4/3.0 mg/kg/day based on decreased body weight (10-13%) and body weight gain (16-25%). **Reproductive NOAEL** (M/F) = 2.4/3.0 mg/kg/day LOAEL (M/F) = 4.8/6.2 mg/kg/day based on decreased live pups/litter in both generations (9.7-9.9 vs. 11.4-11.8 controls). **Offspring NOAEL** (M/F) = 0.5/0.6 mg/kg/day **LOAEL** (M/F) = 2.4/3.0 mg/kg/day based on decreased F_1 and F_2 pup body weight (8-18%) and body weight gain (mid 20-26%; high 40-60%).
870.4100a 83-1a Chronic toxicity (rat)	Satisfied by MRID# 00156739, 41657101 (83-5)	
870.4200 83-2a Carcinogenicity (rat)	40179801b/46274301 (1986) NTP Unacceptable/guideline 0, 38, 75 ppm M: 0, 1.7, 3.4 mg/kg/day F: 0, 1.8, 3.6 mg/kg/day	**NOAEL** (M/F) = 3.4/3.8 mg/kg/day **LOAEL** = not identified Animals could have tolerated a higher dose, MTD not achieved No evidence of carcinogenicity
870.4200 83-2a Carcinogenicity (rat)	00143257 (1979) Unacceptable/non-guideline M&F: 0, 1.7, 3.0 mg/kg/day (i.p., 42 days, observed for 17 months) M&F: 0, 1.7, 3.0 mg/kg/d (gavage, 42 days)	**NOAEL** = 3.0 mg/kg/day **LOAEL** = not identified Animals could have tolerated a higher dose, MTD not achieved No evidence of carcinogenicity

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile of Rotenone[1]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.4200 83-2b Carcinogenicity (mouse)	40179801a/46274301 (1986) NTP Acceptable/guideline 0, 600, 1200 ppm M: 0, 111, 242 mg/kg/day F: 0, 124, 265 mg/kg/day	**NOAEL** = not identified **LOAEL** (M/F) = 111/124mg/kg/day based on decreased body weight (low: (M) 6-12%, (F) 12-20%, high: (M) 1217%, (F) 17-26%. No evidence of carcinogenicity
870.4200 83-2b Carcinogenicity (hamster)	00143256 (1979) Unacceptable/non-guideline 0, 125, 250, 500, 1000 ppm M&F: 0, 10, 21, 42, 83 mg/kg/day (food factor of 0.083)	**NOAEL** = 42 mg/kg/day LOAEL = 83 mg/kg/day based on decreased weight gain. No evidence of carcinogenicity Excessive mortality due to secondary infection; additional groups administered 500 and 1000 ppm for 3 or 4 months were mated resulting in no viable offspring at 1000 ppm and maternal neglect and cannibalization at 500 ppm
870.4300 83-5 Chronic/Oncogenicity (rat)	00156739 (1985) 41657101 (1989 amendment) Acceptable/guideline 0, 7.5, 37.5, 75 ppm M&F: 0, 0.375, 1.88, 3.75 mg/kg/day (food factor of 0.05)	**NOAEL** = 0.375 mg/kg/day **LOAEL** = 1.88 mg/kg/day, based on decreased body weight at termination [M:7% (mid) and 15% (high); F: 24% (mid) and 42% (high)] and cumulative weight gain [M: 10% (mid) and 20% (high); F: 31% (mid) and 55% (high)] and food consumption in females [9% and 21% in mid and high, respectively] No evidence of carcinogenicity
Gene Mutation 84-2 870.5100 (*Salmonella typhimurium*)	40170506 (1988) NTP study Acceptable/guideline	No evidence of induced mutant colonies over background for any tester strain at any concentration up to 10,000 µg/plate with and without metabolic activation; strains TA98, TA100, TA1535, TA1537.
Gene Mutation 84-2 870.5100 (*Salmonella typhimurium*)	40170502 (1978) Acceptable/guideline	No evidence of induced mutant over background for any test strain at any concentration up to 10,000 µg/disk with and without metabolic activation; strains TA98, TA100, TA1535, TA1537, TA1538.
Gene Mutation 870.5300 84-2 (mouse lymphoma cells)	40170505 (1984) Acceptable/guideline	Evidence of a concentration-related positive response of induced mutant colonies over background at 0.25-8.0 µg/mL without metabolic activation; significant cytotoxicity at 4 and 8 µg/mL.
Cytogenetics 870.5375 84-2 (Chinese hamster ovary)	40179801c (1986) Acceptable/guideline	No evidence of chromosome aberrations up to 100 µg/mL without metabolic activation and 250 µg/mL with activation.

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile of Rotenone[1]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
Cytogenetics 870.5385 84-2 (rat and mouse)	00093702 (1981) Unacceptable/non-guideline	Maximum tolerated dose (MTD) was not achieved in either the rat or mouse assays. No evidence of induced chromatid/chromosome aberrations in rat bone marrow cells up to 7.0 mg/kg; no significant increase in frequency of micronuclei in erythrocytes from bone marrow of mice up to 80 mg/kg.
Micronucleus 870.5395 84-2 (mouse)	00093702 (1981) Acceptable/guideline	Negative at oral doses of 0, 10, or 80 mg/kg
Mitotic gene conversion 870.5575 84-2 (*Saccharomyces cerevisiae*)	00144292 (1981) Acceptable/guideline	No evidence of induced mutant colonies over background for any test concentration up to 10,000 ug/plate with and without metabolic activation. Limit dose 5000 µg/plate.
870.6200a 81-8 Acute neurotoxicity screening battery	Not Available	
870.6200b 82-7 Subchronic neurotoxicity screening battery	Requested, DCI 02/09/2004 (GDCI-071003-20980) -inhalation (rat) in reserve	
870.6300 83-6 Developmental neurotoxicity	Study required pending results of the subchronic inhalation neurotoxicity study.	
870.7485 85-1 Metabolism and pharmacokinetics (rat)	00145496 (1984) Acceptable/non-guideline 0.01, 0.1, 5 mg/kg (oral and iv)	Primary route of excretion is in feces; extensive enterohepatic circulation; some urinary excretion with females greater than males; polar metabolites reported in feces, but metabolites not identified
870.7600 85-2 Dermal penetration (rat)	Not Available	
870.7800 Immunotoxicity	Not Available	
Special studies Subacute neurotoxicity (rat)	45279502 (Betarbet et al., 2000) Acceptable/nonguideline M: 2.5-2.75 mg/kg/day by i.v. infusion for 1-5 weeks	Behavioral, biochemical, and neuropathological effects in humans; induction of specific neurodegenerative lesions in nigrostriatal dopaminergic neurons

1 The DERs have not been updated according to current practice.

A.3 Literature Search for Rotenone

As part of registration review for rotenone, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to rotenone via exposure routes relevant to human health pesticide risk assessment not accounted for in the agency's rotenone toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 5045 studies from the literature. During the title/abstract and/or full text screening of these studies, none of the studies were deemed to contain potentially relevant information (either quantitative or qualitative) for the rotenone human health risk assessment. Detailed information regarding the literature review is as follows:

Date and Time of Search: 01/31/2020; 11:07 am
Search Details:
((*Rotenone*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 5045
Number of Swift Articles: 4133 for Animal (all)
Number of Swift Articles: 2127 for Human
Number of Swift Articles: 0 for No Tag

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

Conclusion of Literature Search: Following title/abstract and/or full text screening, no studies were identified as containing potentially relevant information (either quantitative or qualitative) for the rotenone human health registration review risk assessment.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.
**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize studies identified in the PubMed search based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).
Studies could have resulted in multiple tags which would account for citations identified in PubMed not matching the number of tagged citations.

Appendix B. Physical/Chemical Properties

Table B.1: The Physicochemical Properties of Rotenone			
OPPTS Guideline Numbers	**Master Record Identification [MRID]**	**Status[1]**	**Results or *Deficiency**
830.1550 Product Identity and Composition	44111501	A	
830.1600 Description of Materials Used to Produce the Product	44111501	A	
830.1620 Description of Production Process	44111501	A	
830.1650 Description of Formulation Process	44652801	A	
830.1670 Discussion of Formation of Impurities	44111501	A	
830.1700 Preliminary Analysis	44138601	A	
830.1750 Certified Limits	44395301	A	
830.1800 Enforcement Analytical Method	44726501, 44510801 HPLC/UV	A	
830.1900 Submittal of Samples	EPA Repository, Ft. Meade, MD.	A	44.2% --- TIFA, Inc. Expiration Date: 02/22/2006
830.6302 Color	43818002	A	Tan
830.6303 Physical State	43818002	A	Powder
830.6304 Odor	43818002	A	Wet chalk
830.6313 Stability to normal and elevated temperatures, metals and metal ions	44123705	A	Temp(s) = No change was observed; the loss was less than 5%. Metals = No change was observed, the loss was about 5%.
830.6314 Oxidation /Reduction Chemical Incompatibility	43818002	A	None
830.6315 Flammability	43818002	A	Not Applicable
830.6316 Explodability	43818002	A	Not Applicable
830.6317 Storage Stability	44130801	A	**Container / Stability / Duration / Temp.** Poly bag / Stable / 1.0 yr. / 22°C Poly bag / Loss ≤5% / 0.5 yr. / 40°C
830.6319 Miscibility	44130801	A	Not Applicable
830.6320 Corrosion Characteristics	44130801	A	None
830.6321 Dielectric Breakdown Voltage	44130801	A	Not Applicable
830.7000 pH	44130801	A	Not Applicable
830.7050 UV/VIS absorption	(MRID to be assigned)	A	Absorptivity at 235nm & 292 nm
830.7100 Viscosity	44130801	A	Not Applicable
830.7200 Melting Point/Melting Range	44123702	A	160 -163 °C
830.7220 Boiling Point/Boiling Point Range	------	------	PAI is solid at room temperature.
830.7300 Density/Relative Density/Bulk Density	43818002	A	Fluffy 0.2400 g/cm^3; 14.70 lb/cu. ft Compacted 0.4500g/cm^3; 28.10 lb/cu. ft
830.7370 Dissociation Constant	44718101	A	PAI no dissociation constant at pH 2-12. (OECD Method No. 112)
830.7550 Partition coefficient (n-octanol /water) shake flask method	44123704	A	$K_{o/w}$ Log P = 4.16
830.7560 Partition coefficient (n-octanol /water) generator column method	------	------	See Guideline 830.7550
830.7570 Partition coefficient (n-octanol /water) estimation by liquid chromatography	-------	-------	See Guideline 830.7550

Table B.1: The Physicochemical Properties of Rotenone			
OPPTS Guideline Numbers	**Master Record Identification [MRID]**	**Status[1]**	**Results or *Deficiency**
830.7840 Water Solubility: Column Elution Method; Shake Flask Method	44123703	A	Solvent = Water; Temperature = 20 °C; Avg. Solubility = 0.142 mg/ml
830.7860 Water solubility, generator column method	--------	--------	See Guideline 830.7840
830.7950 Vapor pressure	44652901	A	Not Applicable
[1] A = Acceptable; U = Unacceptable (See *Deficiency)			

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include PHED 1.1, the AHETF database, the ORETF, the ARTF database, the Residential SOPs (aquatic SOP) and are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[20].

[20] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure