APPENDIX H: HUMAN HEALTH RISK ASSESSMENT

Toxicity Profile

The Environmental Protection Agency (EPA; 2007A) estimated the degree to which rotenone could cause adverse health effects in humans, and the level or dose at which those effects would occur, evaluating acute, short and intermediate term, and chronic effects. The EPA concluded that "rotenone has high acute toxicity via the oral and inhalation routes of exposure (Category I) and low acute toxicity via the dermal route of exposure (Category IV)," and that "rotenone is not an eye or skin irritant nor is it a skin sensitizer." Based on a structure activity relationship and human dermal information, dermal absorption of rotenone was estimated at 10%, while a default factor of 100% was used for inhalation absorption. Table H-1 (excerpted from the EPA 2007A), shows the acute toxicity profile for rotenone.

Table H-1. Acute toxicity profile for rotenone.

Guideline Number	Study Title	MRID	Results	Toxicity Category
870.1100	Acute oral [rat]	00145496	LD_{50} = 102 mg/kg (M) LD_{50} = 39.5 mg/kg (F)	I
870.1200	Acute dermal [rabbit]	43907501	LD_{50} > 5000 mg/kg	IV
870.1300	Acute inhalation [rat]	42153701	LC_{50} = 0.0212 mg/L (combined) LC_{50} = 0.0235 mg/L (M) LC_{50} =0.0194 mg/L (F)	I
870.2400	Acute eye irritation [rabbit]	42076203	PIS = 3.3 at 1 hr., cleared less than 24 hours	IV
870.2500	Acute dermal irritation [rabbit]	42076204	PIS = 0.08 at 1 hr which decreased to 0 at 72 hours	IV
870.2600	Skin sensitization [guinea pig]	42153702	Not a dermal sensitizer	N/A

(*Source: Table 3, EPA 2007A, pg. 11.*)
LD_{50} = Median Lethal Dose; PIS = primary irritation score

The EPA (2007A) used the toxicological endpoints summarized in Table H-2 as part of the human health risk assessment for rotenone. The EPA (2007A) found that available information on rotenone toxicity supported reregistration. However, their assessment of toxicity from multiple types of exposure (e.g., dietary, dermal, and recreational) was highly conservative, based on "a potentially critical effect (neurotoxicity) at doses to which rotenone users," (i.e., those applying rotenone for fish eradication), "could be exposed." Therefore, the EPA placed a cumulative 1,000x uncertainty factor, which includes a 10x database uncertainty factor (to account for limitations in available rotenone data), a 10x uncertainty factor for intra-species variation, and a 10x uncertainty factor for inter-species variation (i.e., since rotenone has only been tested on certain organisms). In effect, this means that the no observed adverse effect level (NOAEL) in rodent species, the mammalian organisms on which rotenone exposure has been studied, involved substantially higher rotenone concentrations than the hypothetical NOAEL for humans determined by the EPA (2007A).

Another way of calculating exposure risk of a substance involves estimating a margin of exposure (MOE), "which is the magnitude by which the NOAEL of the critical toxic effect exceeds the estimated exposure dose (EED), where both are expressed in the same units: MOE = NOAEL (experimental dose) / EED (human dose)" (EPA 1993). For example, in a study where mice were exposed to rotenone, the NOAEL was 15 mg/kg/day (EPA 2007A). However, since this NOAEL concentration cannot be

extrapolated directly to humans, the 1,000x uncertainty factor was applied, in which 15 mg/kg/day is divided by 1,000 to reach a 0.015 mg/kg/day dietary acute population adjusted dose (aPAD; Table H-2), which, in this case, is the human acute EED. Therefore, the estimated human NOAEL of 15 mg/kg/day divided by the 0.015 mg/kg/day EED = a MOE of 1000. In this case, the uncertainty factor is equivalent to the MOE.

Dietary Risk

To estimate acute dietary exposure to rotenone for humans, the EPA (2007A) considered residues in drinking water and food from piscicidal use in fish management. The estimated drinking water concentration (EDWC) was determined to be 200 ppb, which is the solubility limit of rotenone. Estimated exposure from drinking water considered surface water only because rotenone is not expected to reach groundwater (CDHS 2007), and the estimate is conservative because it assumes water is consumed immediately after treatment with no breakdown or water treatment prior to consumption. Rotenone exposure from food may occur if humans consume fish that survive a treatment, although this type of exposure is unlikely, given the remoteness of locations proposed for treatment, closure of the treatment area during application, and high susceptibility of fish to minute concentrations of rotenone. The EPA estimated acute dietary exposure to rotenone is 0.01117 mg/kg/day, which is 26% less than the aPAD of 0.015 mg/kg/day. Since the EPA is concerned when risk estimates exceed 100% of the aPAD, the EPA concluded that acute dietary risk from rotenone is below the level of concern.

Additionally, the EPA (2007A) determined that the chronic dietary risk assessment would only consider "drinking water for the general population and various population subgroups. The chronic assessment only considered drinking water because chronic exposure from food (consumption of treated fish) is not expected based on rotenone's generally rapid degradation and low propensity to bioaccumulate in fish." For chronic exposures, the EPA determined the drinking water level of concern (DWLOC) at 40 ppb, which is based on the most potentially sensitive subgroup of infants and children. The low DWLOC also assumed that rotenone could reach drinking water intakes, of which there are none in the proposed treatment areas in the Restoration Plan/FEIS. The EPA also discusses that, under normal use (i.e., per label requirements), piscicides dissipate via aqueous photolysis and hydrolysis, and are readily deactivated with potassium permanganate ($KMnO_4$). Finally, the EPA discusses it is likely that drinking water treatment by chlorination, ozonation, or charcoal filtering would deactivate rotenone. Based on the "Thus, the Agency expects no chronic exposures to rotenone in situations where water is either treated with potassium permanganate for deactivation purposes or is subject to an oxidative drinking water treatment regimen." (EPA 2007A, pg. 15).

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Table H-2. Rotenone Toxicological Endpoints.

Exposure Scenario	Dose Used in Risk Assessment, Uncertainty Factor (UF)	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NOAEL = 15 mg/kg/day UF = 1000 aRfD = 15 mg/kg/day / 1000 = 0.015 mg/kg/day	 Acute PAD = 0.015 mg/kg/day	Developmental toxicity study in mouse (MRID 00141707, 00145049) LOAEL = 24 mg/kg/day based on increased resorptions
Acute Dietary (all populations)	An appropriate endpoint attributable to a single dose was not identified in the available studies, including the developmental toxicity studies.		
Chronic Dietary (all populations)	NOAEL = 0.375 mg/kg/day UF = 1000 cRfD = 0.375 mg/kg/day / 1000 = 0.0004 mg/kg/day	 Chronic PAD = 0/0004 mg/kg/day	Chronic/onogenicity study in rat (MRID 00156739, 41657101) LOAEL = 1.9 mg/kg/day based on decreased body weight and food consumption in both males and females
Incidental Oral Short-term (1-30 days) Intermediate-term (1-6 months)	NOAEL = 0.5 mg/kg/day	Residential MOE = 1000	Reproductive toxicity study in rat (MRID 00141408) LOAEL = 2.4/3.0 mg/kg/day [M/F] based on decreased parental (male and female) body weight and body weight gain
Dermal Short-, Intermediate- , and Long-Term	NOAEL = 0.5 mg/kg/day 10% dermal absorption factor	Residential MOE = 1000 Worker MOE = 1000	Reproductive toxicity study in rat (MRID 00141408) LOAEL = 2.4/3.0 mg/kg/day
Inhalation Short-term (1-30 days) Intermediate-term (1-6 months)	NOAEL = 0.5 mg/kg/day 100% inhalation absorption factor	Residential MOE = 1000 Worker MOE = 1000	[M/F] based on decreased parental (male and female) body weight and body weight gain
Canter (oral, dermal, inhalation)	Classification: No evidence of carcinogenicity		

(*Source: Table 4, EPA 2007A, pg. 12.*)
UF = uncertainty factor; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; aPAD = acute population adjusted does; cPAD = chronic population adjusted dose; RfD = reference dose; MOE = margin of exposure; N/A= Not Applicable

Dermal, Incidental Oral, and Inhalation Risk

Recreational Risk

Although rotenone can be applied in public and private waters, it is only permitted for sale to certified applicators (EPA 2007A, Finlayson et al. 2010A). Further, although treatment areas are closed to the public during application, they may be exposed by later recreating in water that was previously treated. The EPA therefore estimated recreational exposure and risk, but only from swimming (dermal and incidental ingestion) because other recreational activities would likely result in significantly less exposure. Recreational risks were calculated through the MOE. MOEs $\geq$1,000 indicate that recreational exposure risks to rotenone would not exceed the EPA's level of concern (LOC) for dermal, incidental oral, and inhalation risk.

For short-term risks to adult swimmers on the same day as a 200 ppb application of rotenone, EPA (2007A) determined the dermal and incidental oral MOEs to be 1,600 and 7,000, respectively, neither of which exceeds the EPA LOC of 1,000. However, for short-term risks to toddler swimmers on the same day as a 200 ppb application of rotenone, the EPA (2007A) determined the dermal, incidental oral, and combined non-dietary MOEs to be 970, 850, and 450, respectively, all of which exceed the EPA LOC of 1,000. The EPA therefore estimated it would take three days in 25ºC water for rotenone concentrations to decrease below the LOC (for MOE = 1,000, rotenone concentration = 90 ppb). The EPA is therefore requiring that swimmers not enter rotenone treated areas until exposures are below the LOC.

Occupational Risk
Workers may be exposed while mixing, loading, or applying rotenone, or when entering previously treated areas. The EPA (2007A) initially estimated handler risks using a long sleeve shirt, long pants, shoes, socks, no gloves, and no respirator. If these estimates exceed the EPA's LOC, they then estimated how personal protective equipment (PPE; such as additional clothing, chemical-resistant gloves, respirator) and management controls such as enclosed cabs, closed mixing/loading systems, and water-soluble packaging) would lower exposure.

The EPA (2007A) used the following scenarios to assess risk to occupational handlers for short-term (1 to 30 days) and intermediate-term (1 to 6 months) exposure: mixer/loader, applicator, and mixer/loader/applicator. Exposures were estimated based on application of liquids and wettable powders via helicopter, boat, backpack, and drip bars. The EPA (2007A) used the Pesticide Handlers Exposure Database (PHED) Version 1.1 (August 1998) to estimate handler exposure, but considers these estimates to be conservative due to several factors.

The EPA (2007A) used rotenone's historic maximum labeled concentration (250 ppb; 0.68 lb. ai/A-ft) and solubility limit (200 ppb; 0.54 lb. ai/A-ft) to estimate occupational handler exposure in standing water, as summarized in Table H-3. Because many risks exceed the EPA LOC (MOEs < 1,000), the EPA is requiring the maximum labeled treatment concentration to be reduced from 250 ppb to 200 ppb, the use of additional PPE including respirators, and other mitigation measures to reduce occupational exposure.

The EPA (2007A) did not assess risk for occupational activities after rotenone applications because any dermal exposure from collecting dead fish and inhalation exposure from volatilization are expected to be minimal.

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Table H-3. Rotenone occupational handler risks at 250 ppb and 200 ppb application rates.

Exposure Scenario	Crop or Target	Application Rate[1]	Area Treated Daily (acres)	Combined MOEs[2]							
				Baseline	G + NR	G,DL + NR	G+ 80%R	G,DL+ 80%R	G + 90%R	G,DL+ 90% R	Eng Cont
Mixing/Loading Liquid Concentrates for Helicopter Applications (1a)	Lakes	0.68	10	3.5	290	350	410	530	430	570	1100
	Lakes	0.68	5	7.1	590	710	810	1100	850	1100	2200
	Lakes	0.54	10	4.5	370	450	510	670	540	710	1400
	Lakes	0.54	5	8.9	740	890	1000	1300	1100	1400	2700
Mixing/Loading Liquid Concentrates for Boat Applications (1b)	Lakes	0.68	100	0.35	29	35	41	53	43	57	110
	Lakes	0.68	50	0.71	59	71	81	110	85	110	220
	Lakes	0.54	100	0.45	37	45	51	67	54	71	140
	Lakes	0.54	50	0.89	74	89	100	130	110	140	270
Mixing/Loading Wettable Powders for Boat Applications (2a)	Lakes	0.68	100	0.25	1.7	1.8	4	4.8	4.8	6	84
	Lakes	0.68	50	0.5	3.4	3.7	8	9.5	9.7	12	170
	Lakes	0.54	100	0.31	2.2	2.3	5.1	6	6.1	7.5	110
	Lakes	0.54	50	0.63	4.3	4.6	10	12	12	15	210
Applying Sprays via Helicopter (3)	Lakes	0.68	10	ND	ND	ND	ND	ND	ND	ND	1800
	Lakes	0.68	5	ND	ND	ND	ND	ND	ND	ND	3600
	Lakes	0.54	10	ND	ND	ND	ND	ND	ND	ND	2300
	Lakes	0.54	5	ND	ND	ND	ND	ND	ND	ND	4600
Applying Sprays via Boat Over-surface Boom Equipment (4)	Lakes	0.68	100	48	48	56	66	82	70	88	130
	Lakes	0.68	50	96	96	110	130	160	140	180	380
	Lakes	0.54	100	61	61	70	84	100	88	110	240
	Lakes	0.54	50	120	120	140	170	210	180	220	480
Mixing/Loading/Applying Liquids with a Backpack Sprayer (using PHED liquid low pressure handwand data (5)	Lakes	0.68	2	0.51	71	77	110	120	110	130	NF
	Lakes	0.54	2	0.51	71	77	110	120	110	130	NF
	Streams	0.000016 lb ai/ft3	10,560 ft long	10	1400	1500	2100	2400	2300	2600	NF
	Streams	0.000013 lb ai/ft3	10,560 ft long	13	1700	1900	2600	3000	2800	3200	NF
Mixing/Loading/Applying Liquids with Closed System Aspirators (PHED: missing/ loading liquid – closed system) (6)	Lakes	0.68	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	110
	Lakes	0.68	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	220
	Lakes	0.54	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	140
	Lakes	0.54	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	270
Mixing/Loading/Applying Liquids with Drip Bars (PHED: mixing/loading liquid) (7)	Streams	0.000016 lb ai/ft3	10,560 ft long	360	30000	36000	41000	53000	43000	57000	110000
	Streams	0.000013 lb ai/ft3	10,560 ft long	440	36000	44000	50000	66000	53000	70000	140000
Mixing/Loading/Applying Wettable Powders with a Backpack Sprayer (using PHED wettable powder low pressure handwand data) (8)	Lakes	0.68	2	ND	2.6	3	4.8	6.1	5.3	7.1	NF
	Lakes	0.54	2	ND	2.6	3	4.8	6.1	5.3	7.1	NF
	Streams	0.000016 lb ai/ft3	10,560 ft long	ND	53	60	96	120	110	140	NF
	Streams	0.000013 lb ai/ft3	10,560 ft long	ND	65	74	120	150	130	170	NF
Mixing/Loading/Applying Wettable Powders with Closed System Aspirators (PHED: mixing/loading liquid closed system) (9)	Lakes	0.68	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	84
	Lakes	0.68	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	170
	Lakes	0.54	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	110
	Lakes	0.54	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	210
Mixing/Loading/Applying Wettable Powders with Drip Bars (PHED: mixing/loading liquid) (10)	Streams	0.000016 lb ai/ft3	10,560 ft long	250	1700	1800	4000	4800	4900	6000	85000
	Streams	0.000013 lb ai/ft3	10,560 ft long	310	2100	2300	5000	5900	6000	7400	100000
Mixing/Loading/Applying Wettable Powders via Powder/Sand/Gelatin Paste (11)	Seeps and Springs	There are currently no data to assess this scenario. EPA believes this scenario would result in minimal exposure due to the amount of rotenone used and the fact that this paste is typically mixed in either a lab under a fume hood or by an individual wearing a respirator.									

(*Source: Table 9, EPA 2007A, pgs. 19-20.*)

[1]Lb ai/A-ft unless otherwise noted

[2]G = Gloves; DL= Double Layer (baseline clothing + gloves); NR = No Respirator; R = Respirator; Eng Cont = Engineering Controls; ND = No Data; N/A = Not Applicable; NF = Not Feasible

Rotenone and Parkinson's Disease

Rotenone has been shown to cause symptoms similar to Parkinson's Disease (PD) in animal studies (Betarbet et al. 2000, 2002). Multiple laboratory studies have shown that rotenone is capable of causing damage to nerve cells, including the production of neurotoxic symptoms, in rodents (Cannon et al. 2009). However, most studies in which animal models were used to induce PD-like symptoms have utilized methods of rotenone exposure (e.g., intravenous, intraperitoneal, or directly onto brain tissue), doses (e.g., 2.75-3.0 mg/kg/day, Cannon et al. 2009; 30-100 mg/kg/day, Inden et al. 2011), and exposure durations (e.g., weeks to months) that are dissimilar to the manner in which humans – especially anyone not directly involved in the application process – could be exposed to rotenone during applications for fish eradication (Finlayson et al. 2012). Conversely, one animal study found that chronic rotenone inhalation (i.e., injecting 2.5 mg/kg of rotenone dissolved in saline solution directly into the sinuses of young rats once per day for 30 days) did not result in any PD-like symptoms (Rojo et al. 2007). Two other studies found that chronic oral administration of rotenone to mice caused neurodegeneration and PD-like effects (Inden et al. 2007, 2011). However, the doses that caused these effects ranged between 10 and 100 mg/kg/day, and the duration of the direct oral dosing lasted between 28 and 56 days (Inden et al. 2007, 2011). Therefore, the concentrations of rotenone that resulted in these effects were dramatically higher than the extremely low concentrations of rotenone to which people could potentially be exposed from fisheries management practices (Finlayson et al. 2012).

The other evidence associating rotenone use with PD comes from numerous case-control studies, in which indirect evidence (e.g., self-reporting of pesticide use/exposure and medical history) has shown a possible correlation between rotenone and increased risk of PD (Gorell et al. 1998, Kamel et al. 2006, Tanner et al. 2011, Liew et al. 2014). However, numerous confounding factors prevent inferring any type of causal relationship with rotenone exposure and PD (Finlayson et al. 2012). For example, study participants received potential exposure to numerous other pesticides, specific levels of exposure for all pesticides were unknown, and the biases resulting from the self-reporting of the individuals willing and able to participate (Brown et al. 2006, Tanner et al. 2011, Finlayson et al. 2012). On the latter point, self-reporting leads to large variability in the reliability and accuracy of the data provided (Brown et al. 2006). For example, participants have widely differing ability to remember (or even know) many details regarding the type of pesticides used, levels of exposure, and methods of exposure, all of which can lead to substantial recall bias that severely limits the ability to draw conclusions or make comparisons between studies (Brown et al. 2006, Finlayson et al. 2012).

Some concerns have also been raised regarding other degradation products derived from cubé resins (plant-based rotenoid pesticides), such as deguelin. At lower concentrations, there is some evidence deguelin can be used to deter cancer in humans (Kim et al. 2008). However, high concentrations injected intravenously into rats led to PD-like symptoms (Caboni et al. 2004). Overall, the studies investigating links between rotenone and PD suggest the following conclusion: when organisms are exposed to chemical compounds administered at concentrations substantially exceeding those allowed, and/or via exposure pathways not allowed, a broad spectrum of deleterious effects may result.

Finlayson et al. 2012 provide the following conclusion concerning the potential relationship between PD and rotenone use for fish eradication:

> "*Collectively, the toxicology and epidemiological studies present no clear evidence that rotenone is causally linked to PD. Even if there were clear evidence, it would have little impact on the current and proposed use of rotenone in fish management. This is because the toxicology studies demonstrating PD-like effects were conducted using routes of exposure (e.g., intraperitoneal or intravenous injection or oral dosing with solvents) and exposure regimes (e.g., weeks to months) not germane to potential human exposure associated with fishery uses. The epidemiological studies on pesticide use by farmers*

> *assessed historical application scenarios that paid little or no attention to personal hygiene, safety, and safety equipment. For the applicator, the use of required PPE will significantly reduce, if not eliminate, exposure. For the general public, restricted access to the treatment area until rotenone subsides to safe levels and the use of potassium permanganate to detoxify water leaving the treatment area will greatly minimize exposure. Although everyone is at some risk of developing PD, the risk of developing PD-like symptoms as a result of rotenone exposure from use in fisheries management is negligible because with recommended care, rotenone exposure has been effectively eliminated."* – pg. 473

In summary, in evaluating this potential risk, the NPS finds no evidence to suggest a connection between the piscicidal application of rotenone and PD.

Risk Characterization

Summary- Conclusion

In summary, rotenone is chemically unstable and rapidly breaks down in the environment to yield water-soluble, non-toxic byproducts. The bodies of vertebrates receiving a sub-lethal dose of rotenone metabolize it to non-toxic excretable substances. Rotenone is not considered to be carcinogenic, and recent experimental findings linking rotenone with Parkinson's disease are not a cause for concern when using EPA-required protocols.

The Re-registration Eligibility Determination for Rotenone (EPA 2007A), therefore, concluded that "currently registered uses of rotenone will not pose unreasonable risks or adverse effects to humans or the environment if the requirements for re-registration outlined in this document are implemented." The EPA also concluded the following: "Provided that registrants comply with the requirements of this RED, the EPA believes that rotenone will not present risks inconsistent with FIFRA and that rotenone's benefits to society, including enhanced recreational areas and control of nonnative and invasive species, outweigh the remaining risks." The EPA further concluded that "continued registration of both liquid and wettable powder rotenone products, subject to the requirements of this RED, would provide benefit to society in controlling invasive or unwanted fish species."

Human Health and Ecological Risk

In the comprehensive assessments conducted as part of the rotenone re-registration process, EPA (2007A) concluded that most risks from rotenone are below the EPA level of concern (LOC). However, they also identified potential actions that could pose unreasonable risks or adverse effects to human or ecological health if left unmitigated. As a result, the EPA is requiring registrants and users of rotenone to implement the following risk mitigation measures, which were amended from EPA (2007A) and the CFT Legumine™ product label (Zoëcon 2015):

1. Deactivate with potassium permanganate to ensure that rotenone effects will not spread beyond the treatment area.

2. The maximum labeled application concentration will be 50 ppb for species with normal sensitivity/tolerance to rotenone.

3. Require additional personal protective equipment, including air-purifying respirators, protective clothing (coveralls, gloves), and eye protection (splash goggles or face shields).

4. The Certified Applicator or designee under his/her direct supervision ensures concentrations of rotenone at drinking water intakes are below EPA's LOC (40 ppb).

5. Placard treatment areas to prohibit 1) recreational access during treatment, 2) swimming for at least three days following treatment, and 3) consumption of dead fish taken from the treatment area.

6. Ensure rotenone products are mixed/loaded in closed systems (except for backpack sprayers with liquid formulations).

7. Apply rotenone below the water's surface (except for aerial and backpack sprayer applications).

8. Limit the use of backpack sprayers to only liquid formulations.

9. Prohibit rotenone from being applied to estuarine/marine environments.

10. Registrants will update product labels to require these measures.

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