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Rotenone Use in Fish Management and Parkinson's Disease: Another Look

Brian Finlayson^a, Rosalie Schnick^b, Don Skaar^c, Jon Anderson^d, Leo Demong^e, Dan Duffield^f, William Horton^g, Jarle Steinkjer^h & Chris VanMaarenⁱ

^a California Department of Fish and Game (retired), Camino, CA, 95709 E-mail:

^b Michigan State University and U.S. Fish and Wildlife Service (retired), La Crosse, WI, 54603-1088

^c Montana Fish, Wildlife and Parks, Helena, MT, 59620

^d Washington Department of Fish and Wildlife, Olympia, WA, 98501

^e New York Department of Environmental Conservation (retired), Vermontville, NY, 12989

^f Forest Service, U.S. Department of Agriculture, Ogden, UT, 84401

^g Idaho Department of Fish and Game (retired), Boise, ID, 83707

^h Norwegian Directorate for Nature Management, Trondheim, N-7485, Norway

ⁱ New York Department of Environmental Conservation, Watertown, NY, 13601

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Rotenone Use in Fish Management and Parkinson's Disease: Another Look

Brian Finlayson*

California Department of Fish and Game (retired), Camino, CA 95709.
 E-mail: briankarefinlayson@att.net

Rosalie Schnick

Michigan State University and U.S. Fish and Wildlife Service (retired), La Crosse, WI 54603-1088

Don Skaar

Montana Fish, Wildlife and Parks, Helena, MT 59620

Jon Anderson

Washington Department of Fish and Wildlife, Olympia, WA 98501

Leo Demong

New York Department of Environmental Conservation (retired), Vermontville, NY 12989

Dan Duffield

Forest Service, U.S. Department of Agriculture, Ogden, UT 84401

William Horton

Idaho Department of Fish and Game (retired), Boise, ID 83707

Jarle Steinkjer

Norwegian Directorate for Nature Management, Trondheim N-7485, Norway

Chris VanMaaren

New York Department of Environmental Conservation, Watertown, NY 13601

All authors are members of the American Fisheries Society's Fish Management Chemicals Subcommittee.

*Corresponding author.

INTRODUCTION

Rotenone is a nonspecific botanical insecticide with some acaricidal properties. As recently as 6 years ago, it was used in home gardens for insect control and for lice and tick control on pets, and historically it has been used in the agricultural production of leafy and fruity vegetables, stone fruits, and berries. Many fish and wildlife agencies in North America, Europe, Africa, Australia, and New Zealand also use rotenone for fish eradications as part of eliminating invasive species and diseases, restoring native species, and managing sports fish (Finlayson et al. 2000, 2010).

Ten years ago, the American Fisheries Society's (AFS) Task Force on Fishery Chemicals (2001) reviewed the avail-

able studies on the relationship between Parkinson's disease (PD) and rotenone. This review focused on the implications to fish managers and centered on an Emory University study by Betarbet et al. (2000). We were concerned that the inaccurate and incomplete reporting of this study and others might lead to unfounded fears associated with using rotenone in fish management. These concerns were not unfounded; the PD issue has been brought up by project opponents over the last decade in an attempt to derail and discredit fish management projects involving rotenone, as recently as 2011 in Utah (U.S. Forest Service 2011) and Arizona (Arizona Game and Fish Department 2011).

Since 2001, many other studies have been completed that suggest that we revisit the issue. As was the case in 2001, there is little doubt that rotenone, given excessive and unrealistic exposure, may cause specific damage to nerve cells, inducing symptoms of neurotoxicity similar to those associated with PD. The quandary remains in how to interpret these studies given that (1) the routes of exposure employed are typically irrelevant to rotenone's use in fish management and (2) the neurological symptoms from rotenone demonstrated in laboratory studies are broader than those typically seen in PD (i.e., cold symptoms can represent many illnesses, including colds). Here we give a broad overview and assessment of the available evidence (detailed information can be found in the referenced studies).

PARKINSON'S DISEASE AND EFFECTS OF ROTENONE EXPOSURE

The U.S. Library of Medicine (in 2012) defines PD as a progressive degenerative neurological disorder characterized by resting tremors, rigidity, inability to maintain posture, and generally slow movement (see <http://ncbi.nlm.nih.gov/pubmedhealth/PMH0001762>). There are two general types of PD. Familial PD may occur early in life and has a clear genetic (inherited) component. Sporadic PD typically occurs in the elderly, and the incidence increases with age. The pathology of PD involves the progressive loss of dopamine-secreting nerve cells in the middle section of the brain (substantia nigra). The loss of the neurotransmitter dopamine in the brain is associated with overt signs of PD.

Most studies have focused on the controversial use of rotenone, using laboratory animal models, largely to understand the pathogenicity of PD for development of effective treatments. These studies began with the work of Betarbet et al. (2000), who, through intravenous injection of rotenone directly into the brain over 5 weeks, produced damage to brain tissue (microscopic deposits of protein referred to as "Lewy bodies") similar in character to that in PD. Other studies have involved high doses or long periods of subcutaneous, intravenous, or direct brain exposures not directly relevant to human health risk.

ENVIRONMENTAL INFLUENCES AND ROTENONE EXPOSURE

The causes of PD are not well understood and, as noted above, development appears to involve both genetic predisposition and environmental factors. Environmental factors may include relatively common agents such as cigarette smoking, consumption of coffee (McCulloch et al. 2008), and agricultural exposure to pesticides (Brown et al. 2006). In terms of exposure to pesticides, the most consistent relationship noted in epidemiological studies was that increased pesticide exposure caused an increased risk (Drechsel and Patel 2008).

The applicator of liquid and powdered rotenone formulations used in fish management is at greatest risk to exposure from oral, dermal, and inhalation routes. However, these routes of exposure have been significantly reduced, if not eliminated. The application of common sense and good personal hygiene practices will prevent oral exposure. Rotenone is not volatile (vapor pressure of 6×10^{-6} Pa; Huntingdon Life Sciences 2007) and, thus, inhalation is an unlikely route of exposure from liquid formulations. Powdered rotenone can become airborne, but full-face respirators and semiclosed application systems are required. Rotenone stemming from the commercial CFT Legumine formulation is poorly absorbed (<0.37%) through human skin (Swan 2007), and chemically resistant gloves and protective coverall clothing are required and, thus, dermal is an unlikely route of exposure for either formulation.

TOXICOLOGY STUDIES

Durkin (2008) reviewed numerous studies on the use of rotenone in developing animal models for PD; he noted that all of the early studies involved routes of exposure (subcutaneous infusion, intravenous administration, or direct instillation into the brain) that were not directly relevant to human health risk. The U.S. Environmental Protection Agency (USEPA 2005b, 2006) also noted that these studies were not directly relevant to human health risk relative to expected exposure. For example, Ferrante et al. (1997) indicated damage to brain tissue in rats from intravenous rotenone exposure, but the damage was not specific to PD. In the highly reported study, Betarbet et al. (2000) noted specific damage to the midbrain of rats from intravenous exposure to rotenone that was similar to that of PD, but many studies have contradicted those findings. More recent studies by Allen et al. (2009) and Drolet et al. (2009) also involved routes of exposure not relevant to human health risk.

Few studies have attempted to expose laboratory animals to rotenone in a manner consistent with human health risk, including absorption through the skin (dermal), through the gut (ingestion), and through the lungs (inhalation). Ingestion, inhalation, and dermal exposures significantly slow down the introduction of chemicals into the bloodstream. Rotenone is poorly absorbed through the human skin and normally has a slow rate of gut absorption, likely reflecting its metabolism and/or rapid breakdown in the gastrointestinal tract (Durkin 2008). Rojo et al. (2007) concluded that inhalation of powdered rote-

none was the most likely exposure route to humans, but these studies failed to show any PD symptoms in rats following intranasal exposure to powdered rotenone for 30 days. Two studies (Inden et al. 2007; Pan-Montojo et al. 2010) assessed the effect of chronic oral administration of high rotenone doses on the pathology of PD in mice. Pan-Montojo et al. (2010) administered a rotenone solution to mice intragastrically with a stomach tube for 1.5 to 3 months. They found that mice treated with rotenone produced some of the neurological effects associated with PD. However, rotenone was dissolved in the solvent chloroform, a central nervous system depressant, which likely increased its absorption into the gut tissue, which otherwise would have been susceptible to breakdown by stomach acids and enzymes. Inden et al. (2007) reported PD-like effects in mice after oral administration of rotenone but recognized that the evidence did not indicate that rotenone causes PD but only that the results suggest that rotenone-treated mice may be useful in understanding the mechanism of dopamine reduction by neurodegeneration in PD.

In addition to the concerns about the practical applicability of the unnatural rotenone exposures in evaluating human health risk, Lapointe et al. (2004), Ravenstijn et al. (2008), Höglinger et al. (2006), Richter et al. (2007), and Durkin (2008) expressed reservations regarding the use of rotenone as an animal model for PD due to the broader spectrum of neurological effects induced by rotenone relative to the narrower spectrum of effects seen in PD. Regardless of the similarities to PD, rotenone can cause neurological damage given excessive doses and exposures.

EPIDEMIOLOGICAL STUDIES

The Agricultural Health Study (Kamel et al. 2006; Tanner et al. 2011) evaluated the previous use of pesticides by farmers and their incidence of PD. Questionnaires were sent to American farmers to gain information on their pesticide use and medical history (Kamel et al. 2006). The study concluded that increased pesticide use was associated with increased PD risk in farmers and that the use of personnel protection equipment (PPE) decreased this risk. From follow-up investigations of these data, Tanner et al. (2011) concluded that rotenone and paraquat use were associated with increased risk of PD. However, the study participants were exposed to many different pesticides, not just rotenone and paraquat, and pesticide exposures were not actually measured; rather, pesticide exposures were based solely on self-reporting methods. Raffaele et al. (2011) discussed the problems associated with using epidemiological data in environmental risk assessments, specifically citing as examples studies on pesticide exposure contributing to the increased risk of PD. They found inconsistent findings between studies, generic categorization of pesticide exposure, and the use of dichotomous exposure categories (e.g., "ever" versus "never"). They also noted the difficulty in using epidemiological studies to evaluate a disease such as Parkinson's where multiple causal factors (genetic susceptibility, age, and environmental exposures) are present.

RISK: FUNCTION OF TOXICITY AND EXPOSURE

The causality of rotenone in PD is highly debatable based on the available information outlined above. Without rotenone exposure, the risk of developing PD from rotenone is eliminated—and exposure to rotenone can be controlled.

The USEPA (2007) reviewed and considered all public health data on rotenone, including those associated with PD, and issued the Reregistration Eligibility Decision for rotenone. The USEPA was concerned about residential and home garden use of rotenone because nonprofessional applicators may apply material without proper PPE utilized by professional applicators. The home garden and residential uses were voluntarily cancelled by the rotenone registrants, yet the piscicidal use of rotenone was approved for reregistration by the USEPA. The USEPA (2005a) reviewed all poisoning incident data on rotenone from 1984 forward prior to clearing it for reregistration and found only four cases that involved either skin or eye effects. Reigart and Roberts (1999) reported that commercial rotenone products have presented little hazard to humans over many decades, with dermatitis and respiratory tract irritation listed as the symptoms of exposure.

To protect the applicators and the public, the USEPA (2007) required mitigation measures to reduce exposure that included the use of semiclosed mixing and application systems, specific PPE and application techniques, and following the AFS's rotenone standard operating procedures manual (Finlayson et al. 2010). PPE such as respirators, outer clothing (coveralls, gloves), and eye protection (splash goggles, face shields) will virtually eliminate exposure and are required for the application of rotenone in fish management. The public is excluded from the treatment area until rotenone residues subside, and rotenone-treated water leaving the treatment area must be detoxified with potassium permanganate (USEPA 2007). Specific information on proper application procedures and safety equipment are found on rotenone labels and in Finlayson et al. (2010). The AFS also provides annual hands-on training for the safe and effective use of piscicides using the rotenone standard operating procedure manual each May at Utah State University in Logan (see <http://www.fisheriessociety.org/rotenone> for current scheduled classes).


CONCLUSIONS

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.

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From the Archives

The fisheries, in my judgment, have reached a point where no half-measure will answer. What is needed is to look the necessities of the case squarely in the face and provide whole some and sufficient remedies, that will put a stop to the destruction and marketing of immature fish of all valuable kinds; and while it gives nature a chance to help repair the mischief already done, will likewise help to secure to the States the benefits of the artificial propagation and planting.

John H. Bissell (1888): Co-operation in Fish-culture, Transactions of the American Fisheries Society, 17:1, 89-100.

From the Archives

Some time since it was my fortune to pass a number of months in Munich, where, through the courtesy of Professor Voit, Director of the Physiological Institute of the University, I was enabled to make some experiments on the digestion of meat and fish by a man and by a dog. Each lived for three days upon haddock and then for three days upon lean meat, beefsteak. The dog was used to such experiments and got on very comfortably indeed. The meat and fish were each cooked with a little lard. He did not take to the fish at first, but after he got used to it seemed to like it. The first attempt with a man was with the same healthy, rather stolid Bavarian laborer, with whom Dr. Rubher's experiments with meat and bread, above referred to, were performed. He bore up very well through the trials with both the fish and the meat, but the assistant discovered at the end that he had surreptitiously eaten sauerkraut, and the experiment was spoiled.

W. O. Atwater (1888): The Digestibility of Fish, Transactions of the American Fisheries Society, 17:1, 69-83.