

**Human Health and Ecological Risk Assessment for the Use  
of Wildlife Damage Management Methods by APHIS-Wildlife  
Services**

**Chapter XXXI**

**USE OF BRODIFACOUM IN WILDLIFE  
DAMAGE MANAGEMENT**

**Draft**

**March 2024**

**Final**

**March 2025**

## Table of Contents

|       |                                                                                              |    |
|-------|----------------------------------------------------------------------------------------------|----|
| 1     | INTRODUCTION .....                                                                           | 5  |
| 1.1   | Use Pattern of Brodifacoum .....                                                             | 5  |
| 2     | PROBLEM FORMULATION .....                                                                    | 11 |
| 2.1   | Physical and Chemical Properties.....                                                        | 11 |
| 2.2   | Environmental Fate .....                                                                     | 11 |
| 2.3   | Hazard Identification.....                                                                   | 12 |
| 2.3.1 | Mechanism of Action and Metabolism.....                                                      | 13 |
| 2.3.2 | Toxicity .....                                                                               | 14 |
| 2.3.3 | Sub-chronic/Chronic Toxicity.....                                                            | 15 |
| 2.3.4 | Developmental and Reproductive Effects .....                                                 | 15 |
| 2.3.5 | Neurotoxicity and Immunotoxicity Effects.....                                                | 15 |
| 2.3.6 | Carcinogenicity and Mutagenicity.....                                                        | 16 |
| 2.3.7 | Endocrine System Effects .....                                                               | 16 |
| 2.3.8 | Toxicity of Other Ingredients .....                                                          | 16 |
| 3     | DOSE-RESPONSE ASSESSMENT .....                                                               | 17 |
| 3.1   | Human Health Dose-Response Assessment.....                                                   | 17 |
| 3.2   | Ecological Effects Analysis.....                                                             | 17 |
| 3.2.1 | Aquatic Effects Analysis .....                                                               | 17 |
| 3.2.2 | Terrestrial Effects Analysis.....                                                            | 18 |
| 4     | EXPOSURE ASSESSMENT .....                                                                    | 20 |
| 4.1   | Human Health Exposure Assessment.....                                                        | 20 |
| 4.1.1 | Identification of Potentially Exposed Human Populations and Complete Exposure Pathways ..... | 21 |
| 4.1.2 | Occupational Exposure Evaluation .....                                                       | 22 |
| 4.2   | Ecological Exposure Assessment .....                                                         | 23 |
| 4.2.1 | Aquatic Exposure Assessment.....                                                             | 23 |
| 4.2.2 | Terrestrial Exposure Assessment .....                                                        | 24 |
| 5     | RISK CHARACTERIZATION .....                                                                  | 26 |
| 5.1   | Human Health .....                                                                           | 27 |
| 5.2   | Ecological Risks .....                                                                       | 27 |
| 5.2.1 | Aquatic .....                                                                                | 27 |
| 5.2.2 | Terrestrial .....                                                                            | 29 |
| 6     | UNCERTAINTIES AND CUMULATIVE IMPACTS .....                                                   | 33 |
| 7     | PREPARERS: WRITERS, EDITORS, AND REVIEWERS.....                                              | 33 |
| 7.1   | APHIS WS Methods Risk Assessment Committee .....                                             | 33 |
| 7.2   | Internal Reviewers.....                                                                      | 35 |

|       |                                                                               |    |
|-------|-------------------------------------------------------------------------------|----|
| 7.3   | Peer Review .....                                                             | 35 |
| 7.3.1 | Peer Reviewers Selected by the Association of Fish and Wildlife Agencies..... | 35 |
| 7.3.2 | Comments .....                                                                | 35 |
| 8     | LITERATURE CITED.....                                                         | 37 |

## EXECUTIVE SUMMARY

Brodifacoum is a toxicant registered to control rodents under a variety of agricultural and nonagricultural uses. The United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Wildlife Services (WS) uses brodifacoum for conservation purposes to eradicate invasive rodents on islands and to control rodents around non-residential manmade structures. APHIS is the registrant for two brodifacoum end use bait products (Brodifacoum-25D Conservation and Brodifacoum-25W Conservation). Both bait products are restricted use pesticides for sale and use by employees of federal agencies responsible for wildlife management or persons working under their authority. Additional brodifacoum products may be registered and used by WS and cooperators under supplemental labels for specific island projects. WS also uses Talon® Weatherblok® XT for rodent control near manmade structures in projects not associated with island conservation.

USDA APHIS evaluated the potential human health and ecological risks from the proposed use of brodifacoum to control island rodent damage; the evaluation also includes WS minor use of brodifacoum in non-island projects. Brodifacoum is a second-generation anticoagulant. Brodifacoum is acutely toxic through oral, dermal, and inhalation exposure routes (Toxicity Category I) and a mild eye irritant (Toxicity Category III). Dermal irritation was not tested because of its high dermal toxicity, but brodifacoum did not cause dermal sensitization. Although the human hazard potential for the technical active ingredient is high, risks from WS use of the brodifacoum bait formulations will be low because of the low toxicity of the baits (0.0025–0.005% brodifacoum) and the anticipated minimal human exposure. Exposure is greatest for workers who handle and apply the bait; however, required use of personal protective equipment by applicators results in low potential for exposure and risk when factoring in available health effects. The potential exposure and risk to the public is low due to the use pattern and label restrictions, as well as the lack of dietary exposure through food, feed, or drinking water.

Ecological risks to aquatic nontarget organisms are low based on the use pattern, available toxicity data, and labeled mitigation measures designed to reduce exposure to aquatic habitats. Risks to terrestrial invertebrates and plants are also low based on available effects data and the method of application. Risk is most significant for sensitive terrestrial nontarget vertebrates, particularly birds, but these risks can be reduced with label requirements and other mitigation measures designed to reduce exposure.

# 1 INTRODUCTION

Brodifacoum is a rodenticide used by the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Wildlife Services (WS) to eradicate invasive rodents for island conservation purposes, as well as control rodents near non-residential manmade structures. This human health risk assessment (HHRA) and ecological risk assessment (ERA) provides a qualitative evaluation of potential risks and hazards to human health and the environment, including nontarget fish and wildlife. The methods used for the human health risk assessment to assess potential human health effects follow standard regulatory guidance and methodologies and generally conforms to methods used by the U.S. Environmental Protection Agency (USEPA) (National Research Council 1983, USEPA 2016b). The methods used for the ecological risk assessment to assess potential ecological risk to nontarget fish and wildlife generally follow USEPA methodologies (USEPA 2016b).

This risk assessment uses a standard approach of first identifying the hazard during problem formulation. Next, the toxicity of the hazard is evaluated in the dose-response assessment, followed by the determination of potential exposure populations and pathways. Lastly, the toxicity and exposure assessment information are integrated into the risk characterization (determining whether there is adverse human health and ecological risk). This risk assessment also includes a discussion of the uncertainties associated with the risk assessment and cumulative impacts.

## 1.1 Use Pattern of Brodifacoum

A variety of brodifacoum baits are currently registered with the USEPA for the control of commensal rodents in structures and areas near human habitats (USEPA 2016c). Brodifacoum is also one of the anticoagulant rodenticides shown to be effective for conservation efforts where invasive rodents are present on islands (Witmer et al. 2007). APHIS is the registrant of two brodifacoum bait formulations that contain 0.0025% weight per weight (w/w) brodifacoum. Brodifacoum-25D Conservation (USEPA Reg. No. 56228-37) is formulated for “dry” environments. Brodifacoum-25D Conservation is susceptible to degradation in wetter environments, so Brodifacoum-25W Conservation (USEPA Reg. No 56228-36) was developed by Bell Laboratories, Inc. (Madison, Wisconsin) for use in “wet” environments. Both formulations are pelleted baits that can be applied using hand spot baiting methods and ground and aerial broadcast applications under their Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3 labels (USEPA 2019a;b).

To date, APHIS has worked with Federal partners such as the U.S. Fish and Wildlife Service (USFWS) and U.S. Air Force (USAF), non-governmental organizations such as Island Conservation (IC), and the bait manufacturer Bell Laboratories to conduct or facilitate applications of these brodifacoum products to islands for rodent eradication projects. APHIS has also registered island-specific supplemental labels with USEPA for these products that allow higher broadcast application rates and additional use sites and hand spot baiting methods for those rodent eradication projects. WS has also worked with Federal partners to conduct monitoring activities following application of brodifacoum products to islands to assess distribution and density of bait, bait availability for targets, and to document non-target effects through carcass searches.

Currently, APHIS has a Brodifacoum-25W Conservation supplemental label registered for eradication of Polynesian (Pacific) rats (*Rattus exulans*) on Wake Atoll by the WS, USAF, and IC, which occurred in summer 2024 (Table 1). Another invasive rodent species that was recently accidentally introduced to Wake Atoll, white-throated woodrats (*Neotoma albigula*), was removed from Wake Atoll at the same time. This was the second invasive rodent eradication project for

Wake Atoll. The first eradication project in 2012 using Brodifacoum-25W Conservation under a supplemental label successfully eradicated the Asian house rat (*R. tanezumi*) but not the Polynesian rat (*R. exulans*) from Wake Atoll.

APHIS also has a current Brodifacoum-25D Conservation supplemental label registered for eradication of house mice (*Mus musculus*) on Midway Atoll National Wildlife Refuge's Sand Island by USFWS and IC (Table 1). However, bait applications for the Midway Atoll house mouse eradication project were discontinued in summer 2023 after the primary broadcast applications and follow up baiting attempts to kill surviving mice were unsuccessful (USFWS 2024).

APHIS has a supplemental label registered for Brodifacoum-25D Conservation to allow USFWS, IC, and WS to conduct an eradication project to remove the black rat (*R. rattus*) from Savana Island near St. Thomas (U.S. Virgin Islands).

Finally, WS currently has the Brodifacoum-25W Conservation Section 3 label registered in the state of Alaska, although it has not been used in Alaska since USFWS used it on St. Paul Island in 2008.

Since 2011, APHIS also registered a supplemental label (now expired) for USFWS and IC to eradicate black rats (*R. rattus*) from Palmyra Island (Brodifacoum-25W Conservation; 1<sup>st</sup> attempt in 2011 succeeded), and two supplemental labels (now expired) for USFWS and IC to eradicate black rats from Desecheo Island (Brodifacoum-25D Conservation; 1<sup>st</sup> attempt in 2012 failed, 2<sup>nd</sup> attempt in 2016 succeeded).

Although WS primarily uses brodifacoum for island conservation projects to eradicate invasive rodents, WS does have minor use of brodifacoum outside of island conservation. Between FY2016 and FY2020, WS applied an annual average of 1.6 pounds of Talon® Weatherblok® XT (Syngenta Crop Protection, LLC, USEPA Registration Number: 100-1055) to control the Norway rat near manmade structures in Tennessee. WS also sold an annual average of 37.8 pounds of Talon® Weatherblok® XT to cooperators for the control of house mice and Norway rats in Texas.

Table 1 APHIS brodifacoum products and supplemental labels for island conservation projects since 2011 (current and expired) and other minor non-island conservation uses of a non-APHIS product.

| Product                                                                                                                                                                                                                                                                          | Bait Application Rate                                                                                                                                                                                                                                                                                                                                                                                                                                                | Use Pattern                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Product name:<br/>Brodifacoum-25W<br/>Conservation</p> <p>Label type: Section 3 label</p> <p>USEPA Registration No.:<br/>56228-36</p> <p>Label version: Nov. 12,<br/>2019</p> <p>Formulation: 0.0025% w/w<br/>brodifacoum, 99.9975%<br/>w/w other ingredients<sup>1</sup></p> | <p>Hand baiting application rate<br/>depend on the application method<br/>and whether treating for rats or<br/>mice.</p> <p>The maximum amount of bait<br/>applied by hand broadcast and/or<br/>aerial broadcast methods for the<br/>first application is 16 pounds<br/>(lb.)/acre (18 kilogram<br/>(kg)/hectare (ha)). A second<br/>broadcast application can be<br/>made 5 to 7 days after the first<br/>application at no more than 8<br/>lb./acre (9 kg/ha).</p> | <p>Control or eradicate invasive rodents<br/>in wet climates on islands or vessels<br/>for conservation purposes.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Tamper-resistant bait stations at all<br/>use sites on the label</li> <li>• Burrow baiting in uninhabited non-<br/>crop areas</li> <li>• Bait bolas (sachets) on uninhabited<br/>grounded or in peril of grounding<br/>vessels; canopy of trees and<br/>shrubs in non-crop areas</li> </ul> <p>Broadcast applications in<br/>uninhabited areas but not on<br/>vessels:</p> <ul style="list-style-type: none"> <li>• Aircraft</li> </ul> |

| Product                                                                                                                                                                                                                                                                                       | Bait Application Rate                                                                                                                                                                                                                                                                                                                                                                              | Use Pattern                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>• Ground-based mechanical equipment</li> <li>• Gloved hand</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p>Product name:<br/>Brodifacoum-25D<br/>Conservation</p> <p>Label type: Section 3 label</p> <p>USEPA Registration No.:<br/>56228-37</p> <p>Label version: Nov. 12,<br/>2019</p> <p>Formulation: 0.0025% w/w<br/>brodifacoum, 99.9975%<br/>w/w other ingredients<sup>2</sup></p>              | <p>Hand baiting application rate depends on the application method and whether treating for rats or mice.</p> <p>The maximum amount of bait applied by hand broadcast and/or aerial broadcast methods for the first application is 16 lb./acre (18 kg/ha). A second broadcast application can be made 5 to 7 days after the first application at no more than 8 lb./acre (9 kg/ha).</p>            | <p>Control or eradicate invasive rodents in dry climates on islands or vessels for conservation purposes.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Tamper-resistant bait stations at all use sites on the label</li> <li>• Burrow baiting in uninhabited non-crop areas</li> <li>• Bait bolas (sachets) on uninhabited grounded or in peril of grounding vessels; canopy of trees and shrubs in non-crop areas</li> </ul> <p>Broadcast applications in uninhabited areas but not on vessels:</p> <ul style="list-style-type: none"> <li>• Aircraft</li> <li>• Ground-based mechanical equipment</li> <li>• Gloved hand</li> </ul> |
| <p>Product name: Talon®<br/>Weatherblok® XT,<br/>Syngenta Crop Protection,<br/>LLC</p> <p>Label type: Section 3 label</p> <p>USEPA Registration<br/>No.100-1055</p> <p>Label version: Feb. 13,<br/>2015</p> <p>Formulation: 0.005% w/w<br/>brodifacoum, 99.995% w/w<br/>other ingredients</p> | <p>Norway and roof rats:</p> <ul style="list-style-type: none"> <li>• Apply 4–22 [(20 g (0.7 oz.)) blocks (usually at intervals of 15–30 ft) per placement</li> </ul> <p>House mice:</p> <ul style="list-style-type: none"> <li>• Apply 1 bait block per placement. Space placements at intervals of 8 – 12 feet. Two blocks may be needed at points of very high mouse activity</li> </ul>        | <p>Control of Norway rats (<i>R. norvegicus</i>), roof (black) rats (<i>R. rattus</i>), and house mice (<i>M. musculus</i>) in and within 100 feet of man-made structures.</p> <p>Tamper-resistant bait stations required in:</p> <ul style="list-style-type: none"> <li>• Residential structures</li> <li>• USDA-inspected facilities</li> <li>• In treatment areas where children, pets, non-target mammals, or birds may access the bait</li> </ul> <p>Bait stations required for all above-ground, outdoor applications</p>                                                                                                                                         |
| <p>Product name:<br/>Brodifacoum-25D<br/>Conservation</p> <p>Label type: Supplemental<br/>label for use on Midway<br/>Atoll National Wildlife<br/>Refuge (Sand Island)</p> <p>USEPA Registration No.<br/>56228-37</p> <p>Expiration date: Dec. 25,<br/>2025</p>                               | <p>Hand baiting application rate depends on the application method.</p> <p>Up to three broadcast (hand and/or aerial) applications at a rate up to 71.3 lb./acre (80 kg/ha) per application may be made under this supplemental label. This maximum broadcast application rate may be locally exceeded along adjacent borders of parallel swaths. If only two broadcast applications are made,</p> | <p>Eradicate house mice (<i>Mus musculus</i>) on Midway Atoll National Wildlife Refuge's Sand Island.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Bait stations</li> <li>• Bait trays and bait bolas</li> </ul> <p>Broadcast applications methods are the same as the parent label above.</p>                                                                                                                                                                                                                                                                                                                                        |

| Product                                                                                                                                                                                                                                                                                                                       | Bait Application Rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Use Pattern                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients <sup>2</sup>                                                                                                                                                                                                                                             | the second application will ideally be made between 14 and 30 days after the first application but may be made between 12 and 32 days after the first application. If three broadcast applications are made, the applications will ideally be made 7 and 12 days after the prior application but may be made between 5 and 14 days following the last application.                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <p>Product name: Brodifacoum-25W Conservation</p> <p>Label type: Supplemental label for use on Wake Atoll</p> <p>USEPA Registration No.: 56228-36</p> <p>Label expiration: Dec. 31, 2026</p> <p>Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients<sup>1</sup></p>                                          | <p>Hand baiting application rate depends on the application method.</p> <p>Up to three broadcast (hand and/or aerial) applications at a rate up to 45 lb./acre (50 kg/ha) per application may be made under this supplemental label. This maximum application rate may be locally exceeded along adjacent borders of parallel swaths. If only two broadcast applications are made, the second application will ideally be made 21 days after the first application but may be made between 14 and 28 days after the first application. A third "middle" broadcast application can be made 5 to 14 days following the first application in cases of high bait disappearance after the first application.</p> | <p>Eradicate Polynesian (Pacific) rats (<i>Rattus exulans</i>) and other invasive rodents on Wake Atoll.</p> <p>Hand spot baiting methods the same as the parent label above, with the inclusion of:</p> <ul style="list-style-type: none"> <li>• Enclosed bait stations (either tubes or bait boxes with lids)</li> <li>• Elevated and floating bait stations</li> <li>• Bait trays</li> </ul> <p>Broadcast application methods the same as the parent label above, with the inclusion of:</p> <ul style="list-style-type: none"> <li>• Unmanned aerial vehicles (UAV)</li> </ul> |
| <p>Product name: Brodifacoum-25D Conservation</p> <p>Label type: Supplemental label for use on Savana Island, St. Thomas, U.S. Virgin Islands</p> <p>USEPA Registration No.: 56228-37</p> <p>Label expiration date: Dec. 31, 2029</p> <p>Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients<sup>2</sup></p> | <p>Hand baiting application rate depends on the application method.</p> <p>Up to two broadcast (hand and/or aerial) applications at a rate up to 26.76 lb./acre (30 kg/ha) per application may be made under this supplemental label. This maximum application rate may be locally exceeded along adjacent borders of parallel swaths. The second broadcast application will ideally be made 24 days after the first application but can be made 14 to 28 days after the first application.</p>                                                                                                                                                                                                             | <p>Eradicate black rats (<i>Rattus rattus</i>) on Savana Island, St. Thomas, U.S. Virgin Islands.</p> <p>Hand spot baiting methods the same as the parent label above, with the inclusion of:</p> <ul style="list-style-type: none"> <li>• Enclosed bait stations (either tubes or bait boxes with lids)</li> <li>• Bait trays and bait sachets</li> </ul> <p>Broadcast application methods the same as the parent label above, with the inclusion of:</p> <ul style="list-style-type: none"> <li>• Unmanned aerial vehicles</li> </ul>                                            |

| Product                                                                                                                                                                                                                                                                                                       | Bait Application Rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Use Pattern                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Product name:<br/>Brodifacoum-25D<br/>Conservation</p> <p>Label type: Supplemental label for use on Desecheo Island, Puerto Rico</p> <p>USEPA Registration No.: 56228-37</p> <p>Expiration date: Apr. 30, 2014</p> <p>Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients<sup>2</sup></p> | <p>Hand application by bait stations up to 16 oz (454 g) per bait station spaced 160 ft (50 m) apart. Check and refill bait stations at least every 7 days for the first 6 weeks of the operation.</p> <p>The first broadcast application rate (applied by hand broadcast or aerial broadcast) is to be targeted at 16 lb./acre (18 kg/ha) on the ground after adjusting the sow rate for the 3-dimensional surface of the island. A second broadcast application is to be targeted at 8 lb./acre (9 kg/ha) on the ground with the interval between applications timed to maximize the probability of baiting weanling rats that survived the first application.</p> | <p>Eradicate roof (black) rats (<i>R. rattus</i>) on Desecheo Island.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Bait stations</li> </ul> <p>Broadcast applications:</p> <ul style="list-style-type: none"> <li>• Aerial</li> <li>• Gloved hand</li> </ul>                                                                         |
| <p>Product name:<br/>Brodifacoum-25W<br/>Conservation</p> <p>Label type: Supplemental label for use on Palmyra Atoll</p> <p>USEPA Registration No.: 56228-36</p> <p>Expiration date: Jul. 31, 2014</p> <p>Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients<sup>1</sup></p>                | <p>Hand baiting application rate depends on application method.</p> <p>Up to two broadcast (air, ground-based equipment, and/or by hand) applications may be made.</p> <ul style="list-style-type: none"> <li>• The first application is to be targeted at 71.3 lb./acre (80 kg/ha) and may not exceed 80.2 lb./acre (90 kg/ha).</li> <li>• The second application may be made 10 to 14 days after the first application and is to be targeted at 66.8 lb./acre (75 kg/ha) and may not exceed 80.2 lb./acre (90 kg/ha).</li> </ul>                                                                                                                                   | <p>Eradicate black rats (<i>R. rattus</i>) on Palmyra Atoll.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Bait stations</li> <li>• Canopy baiting</li> </ul> <p>Broadcast applications:</p> <ul style="list-style-type: none"> <li>• Hand</li> <li>• Aerial</li> </ul>                                                               |
| <p>Product name:<br/>Brodifacoum-25W<br/>Conservation</p> <p>Label type: Supplemental label for use on Wake Atoll</p> <p>USEPA Registration No.: 56228-36</p> <p>Expiration date: Sep. 1, 2014</p> <p>Formulation: 0.0025% w/w brodifacoum, 99.9975% w/w other ingredients<sup>1</sup></p>                    | <p>Hand baiting application rate depends on application method (bait stations or canopy baiting).</p> <p>The broadcast application rate (applied by hand broadcast or aerial broadcast) for the first application may be targeted at 16 lb./acre (18 kg/ha). A second broadcast application may be targeted at 8 lb./acre (9 kg/ha) with the interval between applications timed to maximize the probability of baiting weanling rats that survived the first application.</p>                                                                                                                                                                                       | <p>Eradicate Polynesian (Pacific) rats (<i>R. exulans</i>) and Asian house rats (<i>R. tanezumi</i>) on Wake Atoll.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Bait stations</li> <li>• Canopy baiting</li> </ul> <p>Broadcast applications:</p> <ul style="list-style-type: none"> <li>• Aerial</li> <li>• Gloved hand</li> </ul> |

| Product                                                                                                                                                                                                                                                                                                                               | Bait Application Rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Use Pattern                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Product name:<br/>Brodifacoum-25D<br/>Conservation</p> <p>Label type: Supplemental<br/>label for use on Desecheo<br/>Island, Puerto Rico</p> <p>USEPA Registration No.:<br/>56228-37</p> <p>Expiration date: Nov. 23,<br/>2020</p> <p>Formulation: 0.0025% w/w<br/>brodifacoum, 99.9975%<br/>w/w other ingredients<sup>2</sup></p> | <p>Hand baiting application by bait<br/>stations up to 16 oz (454 g) per<br/>bait station spaced 160 ft (50 m)<br/>apart. Check and refill bait<br/>stations at least every 7 days<br/>during the operation.</p> <p>Up to two broadcast applications<br/>(aerial and/or hand) may be<br/>made, each having 3 different<br/>maximum applications rates<br/>depending on part of the island<br/>being baited:</p> <ul style="list-style-type: none"> <li>• An application targeting the<br/>coastal zone of the island will<br/>be applied at a rate of 27<br/>lb./acre (30 kg/ha), using a<br/>deflector to direct bait away<br/>from the water's edge.</li> <li>• An application targeting the<br/>interior island and offshore<br/>islets will be applied at a rate of<br/>27 lb./acre (30 kg/ha).</li> <li>• An additional application of bait<br/>targeting the coastal/interior<br/>zone overlap, valley floors and<br/>interior cliff faces will be applied<br/>at a rate of 13 lb./acre (15<br/>kg/ha).</li> </ul> | <p>Eradicate roof (black) rats (<i>R. rattus</i>)<br/>on Desecheo Island.</p> <p>Hand spot baiting methods:</p> <ul style="list-style-type: none"> <li>• Bait stations</li> </ul> <p>Broadcast applications:</p> <ul style="list-style-type: none"> <li>• Aerial</li> <li>• Gloved hand</li> </ul> |

<sup>1</sup> Brodifacoum-25W Conservation is formulated for use in wet climates.

<sup>2</sup> Brodifacoum-25D Conservation is formulated for use in dry climates.

References: (USEPA 2011;2015;2019a;b;2021;2022b)

The ground and aerial broadcast rates described in the current and proposed Brodifacoum-25D Conservation and Brodifacoum-25W Conservation supplemental labels may be exceeded under certain scenarios. For ground broadcast applications there may be exceedance of rates along edges of areas missed or excluded during aerial broadcast applications. The supplemental labels also allow for bait application overlap from aerial broadcast applications in flight lines to ensure thorough coverage to all intended areas. The extent of overlap will vary based on site-specific conditions. Overlap may occur in the coastal/interior overlap zone and may also occur along borders of parallel swaths, at the end of swaths where they intercept swaths created by shoreline or other perimeter baiting, and from back baiting. Applicators should minimize areas where applications overlap but should also ensure that they are baiting all areas sufficiently to maximize efficacy.

The Brodifacoum-25D Conservation and Brodifacoum-25W Conservation formulations contain 0.0025% w/w brodifacoum; the Talon Weatherblok XT formulation contains 0.005% w/w brodifacoum. The concentration of the brodifacoum pellets that WS will use for future island rodent eradication projects may change as WS develops or uses alternate formulations registered by other registrants. While the percentage of active ingredient in pellets may increase in future formulations the range of active ingredient application rates per acre is not anticipated to exceed those maximum rates described in this risk assessment. Any increases in the amount of active

ingredient applied per acre would result in a need for the lead federal agency for the project to reevaluate the risk to human health and ecological resources.

## 2 PROBLEM FORMULATION

The following sections discuss physical and chemical properties, environmental fate, and hazard identification for brodifacoum.

### 2.1 Physical and Chemical Properties

Brodifacoum (synonyms: 3-[3-(4'-Bromo-[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one or 3-[(1RS,3RS;1RS,3SR)-3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin; chemical formula:  $C_{31}H_{23}BrO_3$ ; CAS No.: 56073-10-0) is an organic compound with a molecular weight of 523.43 grams per mole (g/mol) and a molecular structure shown in Figure 1 (USEPA 2016c, NCBI 2023).

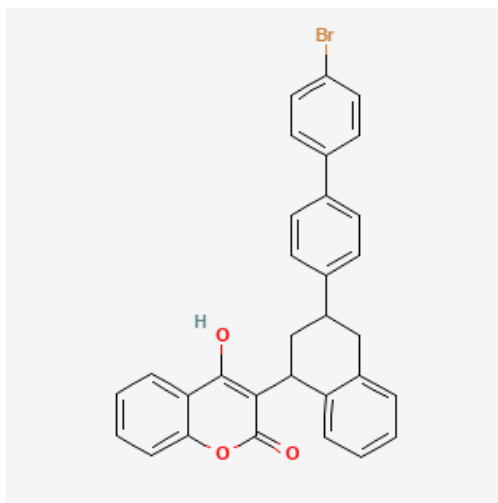


Figure 1. Chemical structure for brodifacoum.

Technical brodifacoum is a cream colored, fine, powdery solid with a melting point of 232°Celsius (C). Under field conditions, brodifacoum is non-volatile. Brodifacoum's estimated vapor pressure is  $1.11 \times 10^{-18}$  mmHg (torr) at 25°C or less than  $10^{-8}$  torr at 20°C. Brodifacoum has a calculated Henry's Law constant of  $2.012 \times 10^{-16}$  atm-m<sup>3</sup>/mole at 25°C, or less than  $10^{-8}$  atm-m<sup>3</sup>/mole at pH 7.4 and 20°C. Brodifacoum's bulk density is 1.42 g/centimeter<sup>3</sup> (cm<sup>3</sup>) at 25°C. Brodifacoum has low water solubility in acidic to neutral waters with increased solubility at alkaline pH values. The water solubility for brodifacoum ranges from 0.0038 milligrams (mg)/Liter (L) at pH 5.2 to 0.24 mg/L at pH 7.4 to 10.0 mg/L at pH 9.3 buffered water at 20°C. Brodifacoum has a high estimated *n*-octanol-water partition coefficient ( $K_{ow}$ ) of  $3.16 \times 10^8$  (log  $K_{ow}$  of 8.5) (USEPA 2016a, NCBI 2023). The soil adsorption coefficient ( $K_{oc}$ ) value was 9,155 L/g-oc (organic carbon) at pH 7.1-7.6 (USEPA 2020b).

### 2.2 Environmental Fate

Environmental fate describes the processes by which chemicals move and degrade in the environment. The environmental fate processes include 1) persistence, degradation, and mobility in soil; 2) movement to air; 3) migration potential to groundwater and surface water; 4) degradation in water; and 5) plant uptake.

Brodifacoum is relatively persistent in soil with a degradation half-life in soil of 157 days in sandy clay loam soil at 21°C (USEPA 1998). Brodifacoum is immobile in soil with a  $K_{oc}$  of >9,155 L/g-oc (USEPA 2016c;2020b). Leaching studies in aged columns of sand, sandy clay loam, silty clay, and clay also indicated that brodifacoum is immobile in soil (USEPA 2016c). Brodifacoum has a low migration potential to groundwater and surface water (USEPA 2016c). Brodifacoum is not readily or inherently biodegradable (USEPA 2016c).

Brodifacoum has a very low vapor pressure ( $1.11 \times 10^{-18}$  mmHg at 25°C) and a low Henry's Law constant value (estimated  $2.012 \times 10^{-16}$  atm-m<sup>3</sup>/mol), suggesting a low potential for volatilization into the atmosphere from soil and water (USEPA 2016c).

Brodifacoum is stable to hydrolysis at pH 5, 7, and 9 (USEPA 2016c). Brodifacoum has the potential to bioaccumulate/bioconcentrate in aquatic environments based on its high  $K_{ow}$  ( $3.16 \times 10^8$ ). The estimated fish bioconcentration factor is 2,450 L/kilogram (kg) wet-weight, with a very slow biotransformation rate (a half-life of 351 days) (USEPA 2016c).

The potential uptake of brodifacoum by plants is low. Most of the bait is expected to be removed by the target species, reducing the amount of brodifacoum available for degradation and leaching into the soil. Brodifacoum is not expected to be available for plant uptake since it binds to soil organic matter rendering it unavailable for uptake (IPCS 2005).

The primary route of dissipation or transportation of brodifacoum appears to be through a food chain where birds, mammals, or other organisms consume bait products, carry the intact chemical within their bodies, and move to offsite locations. During the period of days from exposure to mortality, these poisoned animals become secondary sources for predators and scavengers (USEPA 2016c).

### **2.3 Hazard Identification**

Brodifacoum is an anticoagulant that targets the hematological system with coagulopathy (impairment of clotting) (IPCS 1992, NCBI 2023). The most sensitive toxicity indicator is prothrombin time measurements of bleeding (USEPA 2016a). Toxicity signs are typically hemorrhaging, followed by death. Symptoms in less severe brodifacoum poisoning incidents include excessive bruising, nose and gum bleeding, and blood in the urine and feces (IPCS 2005). In more severe cases, symptoms may include bleeding from several organs within the body, leading to shock and possible death (IPCS 2005).

As a second-generation anticoagulant, brodifacoum is more acutely toxic in a single feeding compared to first-generation anticoagulants and is more persistent in biological tissue. APHIS' two bait formulations contain 0.0025% w/w brodifacoum. Pesticide label statements regarding the human health effects of these bait formulations based on toxicity studies include "*Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes, skin, or clothing.*" (USEPA 2019a;b).

In 2008, USEPA published their Risk Mitigation Decision (RMD) for Ten Rodenticides, with a number of new label mitigations intended to minimize exposure to children and ecological systems, including wildlife (USEPA (2008). In this decision document, four second-generation anticoagulants, including brodifacoum, were prohibited for use in general consumer residential products.

The USEPA Health Effects Division (HED) completed an updated analysis of exposure incidents for 11 anticoagulant and non-anticoagulant rodenticides with outdoor uses, which included brodifacoum, and summarized exposure incidents since the RMD was published (USEPA

2020a;2022a). USEPA reviewed the Incident Data System (IDS), the American Association of Poison Control Centers (AAPCC), the Center for Disease Control's National Institute for Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides database, and the California Pesticide Illness Surveillance Program (PISP) for rodenticide human exposure incidents, including exposure to brodifacoum (USEPA 2022a). The USEPA summary of rodenticide incidents in the AAPCC was not analyzed by rodenticide active ingredient but by first- and second-generation anticoagulant rodenticides.

As per the USEPA HED (USEPA 2022a), the number of second-generation (not limited to brodifacoum) anticoagulant rodenticide incidents reported in the IDS (2009 to 2018) decreased by 79% (from 164 incidents in 2009 to 34 incidents in 2018) and in the AAPCC (2004 to 2017) decreased by 70%. In the AAPCC, the total number of reported child exposures was reduced by 46% between 2011 and 2017 (USEPA 2022a).

In the Main IDS, from January 1, 2015, to July 12, 2019, there were 15 incidents reported that involved brodifacoum; 13 of which involved only brodifacoum and two involved brodifacoum and multiple active ingredients. Twelve incidents were classified as moderate severity, and one incident was classified as major severity (USEPA 2022a). In the Aggregate IDS during the same period, there were 85 incidents reported involving brodifacoum and these were classified as minor severity.

USEPA (2022a) queried the SENSOR database from 2011–2015 and found two instances of brodifacoum incidents. In 2014, one incident involved brodifacoum where the applicator accidentally ingested the product when he forgot to put away his food prior to application. He experienced muscle weakness. In 2011, one incident involved an agricultural worker cleaning a barn; he believed he may have swallowed bait dust. He experienced headache, nausea, and vomiting. These incidents occurred using a product line named d-Con, brodifacoum baits that were cancelled in 2015.

An additional literature review identified human exposure cases from ingestion of brodifacoum with symptoms of generalized ecchymosis, abortion, flank pain, and hematuria followed by epistaxis, gum bleeding, and persistent bleeding for more than two months (NCBI 2023). A case study of brodifacoum exposure in humans reported persistent coagulopathy that lasted approximately one year despite long-term treatment with large dosages of oral phytonadione (vitamin K1), even when brodifacoum was undetectable in the serum (Underwood et al. 2014). One case reported a woman with hemoptysis (coughing up blood) and dyspnea (shortness of breath) following inhalation exposure; she entered an unventilated ceiling space that contained brodifacoum, which was placed approximately two years prior (Love et al. 2019). She estimated she was in the space for about 4 minutes; while there, she noticed the outer coating on the pellets was degraded, showing brodifacoum powder.

WS has had no human adverse incident reports from its limited use of brodifacoum since 2007 for WS personnel or the public.

### **2.3.1 Mechanism of Action and Metabolism**

Brodifacoum is a vitamin-K antagonist that disrupts normal blood-clotting mechanisms and induces capillary damage, leading to death from hemorrhage (USEPA 2004).

Brodifacoum is absorbed through the gastrointestinal tract, skin, and respiratory system (IPCS 2005). The liver is the main organ of accumulation and storage (IPCS 2005). Metabolism studies

measuring recovery of radioactivity following a single oral administration to rats of <sup>14</sup>C-labeled brodifacoum (10 mg/kg-bodyweight (bw)) indicate that considerable radioactivity (approximately 64% of the administered dose) was absorbed and retained in the liver (15%), carcass (43%), and bile (6%) after 48 hours (USEPA 1998;2016c). “After a single oral dose to rats, liver concentrations remained high and relatively constant for 96 hours. Elimination from the liver is slow and biphasic with an initial rapid phase lasting from 2 to 8 days after dosing and a slower terminal phase with an elimination half-life of 130 days.” (IPCS 2005). Following oral administration, brodifacoum is mostly eliminated through feces (IPCS 2005). Brodifacoum has mainly been found as an unchanged compound in feces (IPCS 2005). Approximately 36% of the administered dose was recovered in the feces as unabsorbed. The major (and only identified) metabolite of brodifacoum in bile was the glucuronide conjugate (USEPA 1998). In patients accidentally poisoned with brodifacoum, the plasma half-life was approximately 16–36 days (IPCS 2005).

### 2.3.2 Toxicity

The acute oral, dermal, and inhalation median lethality values (LD<sub>50</sub> and LC<sub>50</sub>) in rats and rabbits indicate that technical brodifacoum is highly toxic (Category I) and is a mild irritant (Category III) when in contact with eyes (Table 2). Dermal irritation was not tested because of its high dermal toxicity. The dermal sensitization study shows that brodifacoum is not a skin sensitizer in guinea pigs.

A 0.25% w/w brodifacoum manufacturing use concentrate product tested in toxicology registration studies called Brodifacoum Formulation Concentrate is moderately toxic (Category II) based on the oral LD<sub>50</sub> and low toxic (Category III) based on the dermal LD<sub>50</sub> (Table 2). Dermal contact can result in severe skin burns or an allergic reaction. This product is 100 times more concentrated than the brodifacoum bait formulations (0.0025% or 0.005%) that WS uses.

Accordingly, the 0.0025–0.005% w/w baits are much less acutely toxic compared to the technical and concentrate formulations (Category IV) (Table 2). The Brodifacoum-25D Conservation and Brodifacoum-25W Conservation safety data sheets (Bell Laboratories 2015b;a) states that contact exposure to the eye will cause moderate irritation.

Table 2. Acute toxicity values of technical brodifacoum used by USEPA to assess acute risk to human health, as well as acute toxicity values for brodifacoum formulations.

| Test                                 | Test Species  | Technical Brodifacoum                                                   | 0.25% w/w Brodifacoum Formulation Concentrate | Talon® Weatherblok® XT 0.005% w/w Brodifacoum | APHIS 0.0025% w/w Brodifacoum Formulations |
|--------------------------------------|---------------|-------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------|
| Acute Oral (LD <sub>50</sub> )       | Rat           | 0.418 mg/kg-bw (M)<br>0.561 mg/kg-bw (F)<br>0.490 mg/kg-bw (both sexes) | 163 mg/kg-bw (M)<br>152 mg/kg-bw (F)          | >5,000 mg/kg-bw                               | >5,001 mg/kg-bw                            |
| Acute Dermal (LD <sub>50</sub> )     | Rabbit or Rat | 5.21 mg/kg-bw (M)<br>3.16 mg/kg-bw (F) (rabbit)                         | >2,000 mg/kg-bw (M, F) (rat)                  | Not available                                 | >5,001 mg/kg-bw (rat)                      |
| Acute Inhalation (LC <sub>50</sub> ) | Rat           | 4.86 µg/L(M)<br>3.05 µg/L (F)                                           | Not available                                 | Not available                                 | Not available                              |

| Test                 | Test Species  | Technical Brodifacoum                   | 0.25% w/w Brodifacoum Formulation Concentrate | Talon® Weatherblok® XT 0.005% w/w Brodifacoum | APHIS 0.0025% w/w Brodifacoum Formulations |
|----------------------|---------------|-----------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------|
| Eye Irritation       | Rabbit        | Minor eye irritation, clearing by day 7 | Iritis clearing by 48 hours                   | Not irritating to eyes                        | Not irritating to eyes                     |
| Dermal Irritation    | Rabbit or Rat | Not available                           | Not irritating to skin                        | Not irritating to skin                        | Not irritating to skin                     |
| Dermal Sensitization | Guinea Pig    | Non sensitizer                          | Not a sensitizer                              | Not available                                 | Not a sensitizer                           |

M = male, F = female

References: (USEPA 1998, Bell Laboratories 2015b;a, USEPA 2016c)

### 2.3.3 Sub-chronic/Chronic Toxicity

During their initial registration review workplan for brodifacoum, USEPA (2016a) determined that a 21-day dermal toxicity study in rats (Guideline 870.3200) and a 28-day inhalation toxicity study in rats (Guideline 870.3465) would be required to maintain brodifacoum registrations, including prothrombin and activated partial thromboplastin time measurements (pre-exposure, and on days 7, 14, and 21/28 of exposure). However, later during registration review, USEPA (2020a) waived these data requirements for the subchronic dermal and inhalation toxicity studies based on a weight-of-evidence approach using the known properties of brodifacoum. Instead, USEPA assumed toxicity for these routes of exposure given that the mode of action and acute toxicity profile are well understood.

### 2.3.4 Developmental and Reproductive Effects

Brodifacoum developmental toxicity studies are available for rats and rabbits. A range-finding study reported 100% maternal mortality at a higher dose of 0.05 mg/kg-bw/day. The subsequent developmental toxicity study in rats at 0, 0.001, 0.01, or 0.02 mg/kg-bw/day did not report developmental effects at the highest dose tested (developmental toxicity no observable adverse effects level (NOAEL) of 0.02 mg/kg-bw/day). The study reported a maternal lowest observable adverse effect level (LOAEL) of 0.01 mg/kg-bw/day based on the finding of blood in the uteri at 0.01 and 0.02 mg/kg-bw/day. The maternal toxicity NOAEL in the study was 0.001 mg/kg-bw/day.

The rabbit developmental study at 0, 0.001, 0.002, and 0.005 mg/kg-bw/day reported significant maternal toxicity (mortality and internal hemorrhage) as well as implantation loss at the maternal toxicity LOAEL of 0.005 mg/kg-bw/day. The LOAEL for developmental toxicity was also 0.005 mg/kg-bw/day based hemorrhagic appearance of fetuses from the three litters available for evaluation. The NOAEL was 0.002 mg/kg-bw/day for both maternal and developmental toxicity. There was no qualitative or quantitative sensitivity seen in the developmental rat or rabbit studies (USEPA 2016a).

USEPA (2016a) waived the requirement for a two-generation reproductive toxicity study in rats based on a weight-of-evidence approach and considering the available hazard and exposure information.

### 2.3.5 Neurotoxicity and Immunotoxicity Effects

USEPA (2016a) also waived the acute and subchronic neurotoxicity considering the available toxicity and exposure information.

A literature review did not identify studies indicating the potential for neurotoxicity from brodifacoum exposure. Kalinin et al. (2017) reported the direct toxic effects of brodifacoum on neurons and glia in an *in vitro* study using an enriched culture of rat cerebellar neurons and cortical astrocytes. After overnight incubation in the study, brodifacoum induced significant cell death in neurons and astrocytes at molar concentrations of 3 micromolar ( $\mu\text{M}$ ) and 30  $\mu\text{M}$ , respectively.

### **2.3.6 Carcinogenicity and Mutagenicity**

A literature search did not identify carcinogenicity studies using brodifacoum. USEPA (2016a) determined that chronic and/or carcinogenicity studies are not required based on brodifacoum's non-food uses and the mutagenicity studies' negative findings.

USEPA (2016a) concluded that brodifacoum is not a mutagen based on the negative results of three mutagenicity studies (a bacterial reverse mutation assay, a mouse micronucleus assay, and a human lymphocyte assay). In the Ames assay with *Salmonella* strains, brodifacoum was negative for inducing reverse gene mutation at the histidine locus at levels up to 5,000 micrograms ( $\mu\text{g}$ )/plate with and without metabolic S-9 activation. The mouse micronucleus assay found that brodifacoum did not induce a clastogenic and/or aneugenic effect in either sex at an intraperitoneal dose of 0.3 mg/kg-bw. A higher dose (0.5 mg/kg-bw) in a preliminary study caused 70% mortality. The *in vitro* cytogenetic assay using human lymphocytes found that brodifacoum was not cytogenic (no increase in the frequency of lymphocyte chromosomal aberrations). Overall, USEPA concluded that brodifacoum has little to no genotoxic activity.

### **2.3.7 Endocrine System Effects**

An Endocrine Disruptor Screening Program (EDSP) was developed to characterize endocrine activity in commercial products, pesticides, and environmental contaminants (USEPA 2023b). EDSP uses a two-tier risk characterization approach consisting of screening candidate compounds for estrogen, androgenic, and thyroid receptor activity and quantifying their impact on environmental and human health (USEPA 2023b). Before 2012, Tier 1 screening involved five *in vitro* and six *in vivo* assays (Browne et al. 2015). To address the growing need for a more rapid but equally comprehensive review of thousands of candidate compounds, the EDSP revised Tier 1 screening to include computational endocrine activity models and high-throughput assays. Tier 2 testing data characterizes the endocrine-related health effects, dose response, and health risks of candidate compounds and substances. Although brodifacoum is listed in the EDSP Universe of Chemicals (USEPA 2012;2023a), brodifacoum was not screened for estrogen receptor bioactivity.

A literature search did not identify any mammalian studies indicating the potential of brodifacoum to affect the endocrine system. Brodifacoum is not among the group of pesticide active ingredients on the initial and secondary lists to be screened under the USEPA EDSP (USEPA 2024b). However, both lists were generated based on exposure potential and not whether the pesticide is a known or likely chemical to disrupt the endocrine system (USEPA 2024b). Brodifacoum is not on the European Union (EU) list of chemicals with the potential to impact the endocrine system (ECHA 2023, The Danish Environmental Protection Agency 2024). The EU list includes three categories: Category 1 – endocrinal effect recorded at least on one type of animal; Category 2 – a record of biological activity *in vitro* leading to disruption; and Category 3 – not enough evidence or no evidence data to confirm or disconfirm endocrinal effect of tested chemicals (Hrouzková and Matisova 2012).

### **2.3.8 Toxicity of Other Ingredients**

The remaining 99.995 and 99.9975% w/w of the brodifacoum bait product formulations are “other” or inert ingredients (e.g., (USDA APHIS 2009, USEPA 2019a;b, HACCO 2021). The identity and safety profile of inert ingredient contents of brodifacoum formulations are not presented on labels

or safety data sheets. These ingredients are considered confidential business information and not generally available to the public. However, they still must be approved inert ingredients for non-food use pesticides by USEPA (2023c).

### **3 DOSE-RESPONSE ASSESSMENT**

#### **3.1 Human Health Dose-Response Assessment**

A dose-response assessment evaluates the dose levels (toxicity criteria) for potential human health effects, including acute and chronic toxicity. USEPA did not establish a tolerance for brodifacoum because there is no registered food or feed uses. The maximum contaminant level has not been established for drinking water. USEPA did not establish an oral reference dose for brodifacoum because USEPA does not believe that the potential exists for significant oral exposure to occupational workers or to the public from incidental exposures from food or drinking water.

For occupational dermal exposure to brodifacoum baits, USEPA (2016a) proposed using a NOAEL of 2 µg/kg-bw/day based on prothrombin time and a LOAEL of 5 µg/kg-bw/day from the developmental study in rabbits as the endpoint in their short- and intermediate-term dermal exposure risk evaluation. The reported LOAEL in the study was based on 75% mortality associated with hemorrhage in pregnant females. The occupational level of concern (LOC) for margin of exposure (MOE) was 1,000 using an uncertainty factor (UF) of 10x for extrapolation from animal to human (interspecies), an UF of 10x for potential variation in sensitivity among members of the human population (intraspecies), and an UF of 10x to account for the absence of key data (i.e., lack of a critical dermal study). USEPA used a dermal short- and intermediate-term dermal absorption factor of 5% to be conservative based on the available data.

However, later in registration review, USEPA determined that a quantitative risk assessment was not necessary for occupational dermal and inhalation exposure, as any potential exposure may result in adverse effects and potential risks of concern (USEPA 2020a). USEPA proposed to require additional personal protective equipment (PPE) on labels to minimize occupational exposure in the future (USEPA 2020a).

In another risk assessment, the average fatal dose for a (60 kg-bw) man was estimated to be 15 mg brodifacoum or 300 g of 0.005% bait (IPCS 2005).

#### **3.2 Ecological Effects Analysis**

This section summarizes available brodifacoum toxicity data for aquatic and terrestrial species. Data searches included the primary literature, unpublished reports, and databases to find representative effects data for aquatic and terrestrial species.

##### **3.2.1 Aquatic Effects Analysis**

Brodifacoum is considered highly toxic to warmwater and coldwater fish species. Acute LC<sub>50</sub> values range from 0.033 mg/L for the rainbow trout (*Oncorhynchus mykiss*) to 0.15 mg/L for bluegill (*Lepomis macrochirus*) in 96-hour acute exposure toxicity tests (Table 3). Toxicity data for marine species is limited; however, available data for freshwater fishes shows that brodifacoum could be toxic to marine fishes. Riegerix et al. (2020) exposed the marine fish species, red-toothed triggerfish (*Odonus niger*) and black triggerfish (*Melichthys niger*), to brodifacoum using a single intraperitoneal injection. These types of exposures have limited use in risk assessments due to method of administration of the test chemical, but the study demonstrated that brodifacoum toxicity is similar between marine and freshwater fish species when dosed using similar methods. The study originally tried oral exposures; however, neither

fish species would consume bait pellets. Fish were also dosed with brodifacoum using oral gavage but regurgitated the bait pellets. This suggests that these fish species will not preferentially consume bait pellets that inadvertently enter the marine environment.

Sublethal effects on fish from brodifacoum exposure have also been observed in short- and long-term laboratory toxicity testing. Wu et al. (2023) reported adverse effects on zebrafish, *Danio rerio*, in six and 96-hour exposures to brodifacoum at 0.8 mg/L. Morphological impacts were noted at 0.8 mg/L in the 96-hr exposures. Effects noted at 0.8 mg/L in both exposure durations include decreases in heart rate, survival, body length, and spontaneous movements. No significant effects were noted at the 0.2 and 0.4 mg/L concentrations. Driessnack et al. (2023) reported lethal and sublethal impacts to Coho salmon (*Oncorhynchus kisutch*) in 76-day exposures to 25 mg/kg brodifacoum bait pellets. Coho salmon embryos were exposed to brodifacoum pellets from fertilization through hatching in a flow-through water system. In the presence of brodifacoum pellets there were significant adverse effects to embryo and alevin survival and development, with pronounced cranial hemorrhaging.

Brodifacoum is considered highly toxic to aquatic invertebrates based on the available toxicity data for the freshwater cladoceran, *Daphnia magna*. The reported median effective concentrations (EC<sub>50</sub>) in a 48-hour exposure range from 0.24 to 0.88 mg/L (USEPA 1991, EU 2016) (Table 3). Marine invertebrate toxicity data is unavailable; however, brodifacoum is considered toxic to marine invertebrates, including corals, based on available studies for freshwater invertebrates. Available toxicity data for other pesticides show that coral sensitivity is within the range of other aquatic freshwater and marine invertebrate toxicity data for various insecticides, herbicides, and fungicides (van Dam et al. 2011, Flores et al. 2020). Barkman and Richmond (2022) reported sublethal impacts to rice coral, *Montipora capitata*, exposed to bait pellets after exposure to 10 and 100 µg/L brodifacoum. Sublethal effects were not observed at the lowest test concentration of 1 µg/L.

Table 3. Brodifacoum acute toxicity in aquatic species.

| Test Species          | Scientific Name            | LC <sub>50</sub> /EC <sub>50</sub> (mg a.i./L) | Reference             |
|-----------------------|----------------------------|------------------------------------------------|-----------------------|
| Freshwater Cladoceran | <i>Daphnia magna</i>       | 0.24–0.88                                      | (USEPA 1991, EU 2016) |
| Rainbow trout         | <i>Oncorhynchus mykiss</i> | 0.033                                          | (USEPA 1991)          |
| Bluegill              | <i>Lepomis macrochirus</i> | 0.15                                           | (USEPA 1991)          |

Brodifacoum is considered toxic to algae with a reported EC<sub>50</sub> of 0.04 mg/L for the freshwater green algae (*Raphidocelis* (formerly *Pseudokirchneriella*) *subcapitata*). The effects were based on negative impacts to growth in a 72-hour exposure toxicity study (EU 2016).

### 3.2.2 Terrestrial Effects Analysis

This section of the ecological effects analysis summarizes available brodifacoum terrestrial toxicity data for mammals, birds, reptiles, and amphibians. This section also summarizes available effects data for terrestrial invertebrates and plants. There are several acute toxicity data values for various species in review documents that cite older studies. These review documents are cited with the reported values to demonstrate the range of sensitivities between species.

#### 3.2.2.1 Mammals

Brodifacoum is considered very highly acutely toxic to mammals in oral exposures. Oral toxicity values range from 0.42 mg/kg-bw for the rat to greater than 25 mg/kg-bw for sheep (Table 4). Acute dermal and inhalation toxicity is also high for mammals (Table 2). Sublethal effects include hemorrhaging, weight loss, decreased activity levels, loss of equilibrium, and lethargy (USEPA 2020b)

Table 4. Brodifacoum acute oral and dietary toxicity to mammals.

| Test species | Scientific Name          | Test                                            | Reference           |
|--------------|--------------------------|-------------------------------------------------|---------------------|
| Rat          | <i>Rattus norvegicus</i> | LD <sub>50</sub> Acute oral: 0.42 mg/kg-bw      | (USEPA 2004;2020b)  |
| Rat          | <i>Rattus norvegicus</i> | LC <sub>50</sub> Acute dietary: 0.55 mg/kg-diet | (USEPA 2004;2020b)  |
| Meadow vole  | <i>Microtus</i> sp.      | LC <sub>50</sub> Acute dietary: 1.4 mg/kg-diet  | (USEPA 2020b;2024a) |
| Mink         | <i>Mustela</i> sp.       | LD <sub>50</sub> Acute oral: 9.2 mg/kg-bw       | (USEPA 2004)        |
| Cat          | <i>Felis catus</i>       | LD <sub>50</sub> Acute oral: ~25 mg/kg bw       | (USEPA 2004)        |
| Sheep        | <i>Ovis aries</i>        | LD <sub>50</sub> Acute oral: >25 mg/kg-bw       | (USEPA 2004)        |

Short- and long-term exposure to brodifacoum results in various sublethal effects that are summarized in Sections 2.3.3 through 2.3.8 of this risk assessment.

### 3.2.2.2 Birds

Brodifacoum is very highly toxic to birds. The lowest reported acute oral LD<sub>50</sub> for birds is 0.26 mg/kg-bw for the mallard (*Anas platyrhynchos*), and the lowest reported subacute median lethality dietary concentration (LC<sub>50</sub>) is 0.8 mg/kg-diet for the bobwhite (*Colinus virginianus*) (USEPA 2020b) (Table 5). Birds exposed to sublethal concentrations exhibit various symptoms such as hemorrhaging, weight loss, decreased activity levels, wing droop, loss of equilibrium, lethargy, and other sublethal effects. No chronic or reproductive avian studies are available for brodifacoum.

Table 5. Brodifacoum toxicity to birds.

| Test species         | Scientific Name            | Test                                               | Reference                            |
|----------------------|----------------------------|----------------------------------------------------|--------------------------------------|
| Mallard              | <i>Anas platyrhynchos</i>  | LD <sub>50</sub> Acute oral: 0.26 mg/kg-bw         | (USEPA 2020b)                        |
| Mallard              | <i>Anas platyrhynchos</i>  | LC <sub>50</sub> Subacute dietary: 2.7 mg/kg-diet  | (USEPA 2020b)                        |
| Japanese Quail       | <i>Coturnix japonica</i>   | LD <sub>50</sub> Acute oral: 11.6 mg/kg-bw         | (USEPA 2024a)                        |
| Bobwhite             | <i>Colinus virginianus</i> | LC <sub>50</sub> Subacute dietary: 0.80 mg/kg-diet | (USEPA 2020b)                        |
| Ring-necked Pheasant | <i>Phasianus colchicus</i> | LD <sub>50</sub> Acute oral: 0.545 mg/kg-bw        | USEPA 1992 as cited in (USEPA 2024a) |

### 3.2.2.3 Reptiles and Amphibians (terrestrial phase)

The limited data on brodifacoum effects on turtles shows low toxicity. Mauldin et al. (2020) administered brodifacoum by oral gavage to painted wood turtles (*Rhinoclemmys pulcherrima*) twice over a seven-day period and monitored for acute and sublethal impacts for 14 days. Wood turtles administered the low concentration (160 µg/mL; range 0.0914–0.119 mg/kg-bw) and high concentration (1,605 µg/mL; 0.888–1.131 mg/kg-bw) brodifacoum solutions did not exhibit acute lethal or sublethal effects. Both gavage solution concentrations exceeded the solubility limit for brodifacoum in water and would not occur in water bodies.

In another study, painted wood turtles were fed even higher brodifacoum doses (1.6 mg/kg-diet). No turtles died or showed signs of ill health prior to being euthanized one week later. The turtle with the highest liver residue level (2.02 parts per million (ppm)) weighed 0.7 lb. (319 g), indicating it received about 500 ppm (0.5 mg) of brodifacoum, which is the equivalent of 20 pellets of Brodifacoum-25D Conservation (0.0025% w/w (25 ppm)) (USFWS 2011).

Weir et al. (2016) reported an LD<sub>50</sub> value of greater than 1,750 mg/kg-bw in a 14-day study using the western fence lizard (*Sceloporus occidentalis*). This study demonstrated lower toxicity of brodifacoum to lizards when compared to mammals and birds.

Mauldin et al. (2020) dosed green iguanas (*Iguana iguana*), giant ameivas, or South American ground lizard, (*Ameiva ameiva*) and boa constrictors (*Boa constrictor*) twice over a seven-day period and monitored for acute and sublethal impacts for 14 days. Three ameivas died in the low dose brodifacoum treatment level (0.134–0.183 mg/kg-bw) and one in the high dose (1.339–1.781 mg/kg-bw). One iguana in the low brodifacoum treatment level died (0.242–0.321 mg/kg-bw); however, no mortality was observed in the high brodifacoum dose level (2.293–3.178 mg/kg-bw). Iguanas at low and high doses following treatment showed markedly dark coloration that is frequently considered a sign of stress. There was no change in coloration noted in the control animals. Several treated ameivas were notably lethargic or unresponsive following dosing, which was not observed in the controls. No mortalities or behavioral effects were noted in low or high doses administered to boa constrictors.

#### **3.2.2.4 Terrestrial Invertebrates and Microorganisms**

Effects data are limited for terrestrial invertebrates, but earthworm, snail, and crab exposures show low toxicity after exposure to high concentrations of a brodifacoum formulation in laboratory toxicity testing (Booth et al. 2003). USEPA (2020b) reports the results from an earthworm study where the *Eisenia foetida* 14-day LC<sub>50</sub> (mg/kg-soil) was greater than 994 mg/kg-soil, suggesting low toxicity. Pain et al. (2000) also demonstrated low brodifacoum toxicity to the hare-lipped land crab (*Johngarthia* (formerly *Gecarcinus*) *lagostoma*). However, on Palmyra Atoll, some fiddler crabs (*Uca tetragonon*) may have died from brodifacoum poisoning in conjunction with the rat eradication (Pitt et al. 2015). USEPA (2020b) pesticide incident reporting suggests a low number of crab mortalities associated with SGAR use.

#### **3.2.2.5 Terrestrial Plants**

No toxicity data appears to be available testing the effects of brodifacoum on terrestrial plants. Acute and chronic adverse effects on terrestrial plants are not anticipated based on the mode of action of brodifacoum, low bioavailability in soil, and a lack of a similar pathway in plants.

## **4 EXPOSURE ASSESSMENT**

### **4.1 Human Health Exposure Assessment**

WS uses Brodifacoum-25W Conservation and Brodifacoum-25D Conservation to assist other Federal agencies and U.S. Territories with rat and mouse eradication for island conservation purposes. These pelleted formulations are restricted use pesticides, thus only certified applicators or persons under their direct supervision who are employees or under direct supervision of federal agencies responsible for wildlife management may use the product. WS also uses limited amounts of Talon Weatherblok XT, a paraffin wax block formulation, to control Norway rats and house mice. The Weatherblok label requires the use of tamper-resistant bait stations in residential structures, USDA-inspected facilities, and treatment locations accessible to children, pets, and nontarget mammals and birds. For all above ground outdoor applications, bait stations are required. In addition, the Weatherblok label only allows applications in and within 100 feet of manmade structures.

Exposure assessments estimate the potential exposure of humans to brodifacoum. An identified exposure pathway for brodifacoum includes (1) a release from a source, (2) an exposure point where contact can occur, and (3) an exposure route such as ingestion, inhalation, or dermal contact (USEPA 1989). Exposures for the identified human populations are qualitatively evaluated for each identified exposure pathway.

#### **4.1.1 Identification of Potentially Exposed Human Populations and Complete Exposure Pathways**

Based on the expected WS use pattern and label restrictions for brodifacoum applications, workers applying brodifacoum in the field are the most likely subgroup of the human population to be exposed to brodifacoum. Exposure during transportation is not anticipated because the material is sealed. Brodifacoum formulations are ready to use with no mixing required. The label application methods include tamper-resistant bait stations, burrow baiting, canopy baiting with bait sachets, and aerial and ground broadcast baiting, with broadcast baiting having the greatest potential for human exposure. Supplemental labels may allow additional hand spot baiting application methods on an island-by-island basis. For example, the current Brodifacoum-25D Conservation and Brodifacoum-25W Conservation supplemental labels for use on Wake Atoll and Midway Atoll National Wildlife Refuge list the use of bait trays, and the current Brodifacoum-25W Conservation supplemental label for Wake Atoll allows the use of elevated and floating bait stations.

The current labels for Brodifacoum-25D Conservation and Brodifacoum-25W Conservation Section 3 labels do not allow broadcast applications in areas of human habitation or over human residences. Ground or aerial broadcast applications of brodifacoum formulations is prohibited by the label in areas of human habitation unless allowed by USEPA for specific island projects under supplemental labels (USEPA 2019a;b;2021;2022b). When a conservation project does occur on an island with a permanent residential community, such as in the case of Wake Atoll and Midway Atoll National Wildlife Refuge, additional protection measures requirements may be implemented as part of the supplemental label or in project planning. For example, the below mitigation measures will be used to protect human health from brodifacoum applications that are planned for rodent eradication at Wake Atoll:

- Residents will be informed of the project activities, including rodenticide use and risks, the planned application methods, potential pathways of the toxins, and requirements for reporting incidents during and after the application process that might have deviated from the application plan (e.g., bait spillage).
- Pre- and post-test water sources and marine food sources to determine any risks to staff.
- Post warning signs before, during, and after a bait application.
- Medical staff will be equipped and trained (as needed) to assess prothrombin and other potential indices of anticoagulant poisoning.
- Cover wells and water tanks during aerial broadcast applications. Alternately, hand broadcast applications, bait stations, bait trays, and bait sachets can be used around wells and water tanks.
- Recommend a three-month consumption prohibition for fish caught in the lagoon.
- Incinerate recovered rat carcasses, where feasible.

Implementation of the above mitigation measures in areas of human habitation for future brodifacoum island conservation uses will be site specific and may include other measures where appropriate. Any of these measures would be part of a supplemental label for such uses where there is a proposal to broadcast apply brodifacoum in areas of human habitation.

The potential for exposure from the proposed WS use pattern is low, however accidental exposure may occur during application. The risk of exposure via ingestion or inhalation is minimal due to outdoor use and label application restrictions and PPE.

A significant direct exposure pathway to the Brodifacoum-25D Conservation and Brodifacoum-25W Conservation formulations used by WS is not identified for the public because this product is a restricted use pesticide and can only be sold to certified applicators that are employees of federal agencies responsible for wildlife management for conservation uses on islands. The brodifacoum formulations can only be applied by a certified applicator or persons under their direct supervision. Belowground burrow baiting is only permitted in uninhabited non-crop areas. Bait sachets may be used within and around institutional structures, within and around uninhabited man-made structures, around the perimeter of hydroponic gardens or greenhouses, freshwater tanks, seeps, pools, and ponds, and all other non-crop areas on islands, including canopies of trees and shrubs and subterranean spaces. Enclosed bait stations may be used within and around any man-made structure, within and around non-operational ventilation ducts, around the perimeter of freshwater tanks, seeps, pools, and pods, and all other non-crop areas on islands.

Similarly, a significant direct exposure pathway to Talon Weatherblox XT formulation used in by WS is not identified for the public due to the label's application restrictions and WS use patterns.

As a result of these use restrictions for brodifacoum formulations used by WS, the public is not considered a vulnerable population for direct exposure to brodifacoum used by WS.

Although oral exposure to all formulations of brodifacoum is acutely hazardous, label restrictions render accidental dietary exposure an incomplete exposure pathway. Brodifacoum is a non-food use chemical with no anticipated drinking water exposures based on label restrictions.

Brodifacoum is immobile in soil, and mobility into nearby water bodies or aquifers is not expected. In addition, label restrictions state that no applications are allowed directly to water, areas where surface water is present, or intertidal areas below the mean high-water mark (except for elevated and floating bait stations used in island conservation) (USEPA 2019a;b;2021;2022b). Placement of elevated and floating bait stations is allowed in intertidal zones above the mean low tide mark and below the mean high tide water mark on the current supplemental label for Wake Atoll. In addition to these restrictions, floating bait stations may only be used where the water is calm enough that the bait stations will not be inundated with water or capsize; the stations must be tethered or attached to a stationary object. The supplemental label requires floating bait stations in intertidal zones be removed if stormy weather is forecasted.

Brodifacoum has a low potential for volatilization due to its low vapor pressure. As a result of these label restrictions and brodifacoum's environmental fate properties, surface and groundwater exposure pathways are also incomplete.

#### **4.1.2 Occupational Exposure Evaluation**

This section qualitatively evaluates worker exposures from a direct contact pathway while applying baits. USEPA (2020a) finds that "for loose formulations, occupational dermal and inhalation exposures are anticipated for handlers (e.g., application by hand, handheld, ground/aerial equipment)." Brodifacoum's chemical properties (molecular weight of 523.4 g/mol and log  $K_{ow}$  of 8.5) indicate a low potential for dermal adsorption (USEPA 2016a).

Following label directions, including the use of PPE, will minimize worker exposure to brodifacoum via inhalation and dermal contact routes. Proper PPE for applicators, other handlers, and anyone who retrieves carcasses or unused bait of Brodifacoum-25D Conservation and Brodifacoum-25W Conservation formulations include long pants, shoes plus socks, and barrier laminate gloves. Applicators performing aerial applications Brodifacoum-25D Conservation and Brodifacoum-25W Conservation formulations, and persons retrieving unused bait following aerial applications must additionally wear protective eyewear or face shield and a minimum of a NIOSH-approved

respirator (specifics provided on the labels). Proper PPE for applicators, other handlers, and anyone retrieving carcasses or unused bait for Talon Weatherblok are similar, however require the use of waterproof gloves in place of barrier laminate gloves (USEPA 2019a;b;2021;2022b).

WS may monitor treatment sites for impacts to target and non-target species. Personnel that conduct posttreatment monitoring follow applicable standard operating procedures and pesticide labels that include appropriate PPE for posttreatment activities. Before monitoring, WS train personnel in the proper handling of animals and use of PPE. Monitoring does not occur during treatment so exposure to brodifacoum during treatment would not occur. Personnel wear PPE when handling live animals and animal carcasses and when handling bait pellets in the environment. Based on these safeguards, monitoring activities are unlikely to pose health and safety concerns for personnel or the public.

## **4.2 Ecological Exposure Assessment**

This section provides a qualitative assessment of the exposure of nontarget terrestrial and aquatic organisms from brodifacoum applications.

The application method will affect nontarget species' primary and secondary exposure potential. Depending on the formulation used for treatment, the label may allow for applications belowground by hand, bait bolas, in tamper-resistant bait stations, or through aerial and ground broadcast applications.

### **4.2.1 Aquatic Exposure Assessment**

The labels for brodifacoum formulations do not allow applications to water bodies. Island conservation applications of brodifacoum are made in a manner that will reduce the likelihood of pesticide deposition into aquatic areas such as interior waterbodies and the outer coastline of islands. The following additional restriction statements are examples of mitigation measures that have been implemented in previous island conservation applications to reduce the likelihood of aquatic exposure:

- No broadcast bait applications over uncovered, inland waterbodies.
- No rodenticide applications below the mean high tide water line except for floating and elevated bait stations, which can be placed between the mean low tide and mean high tide water lines in areas with no predictable wave action.
- No broadcast applications within 3.3 ft (1 m) of the water's edge for uncovered, inland, freshwater bodies.
- Use of a deflector shield (helicopter), directional spreader (Uncrewed Aerial Vehicle (UAV)), or narrow swath bucket (helicopter or UAV) for aerial broadcast applications adjacent to waterbodies or along the coastal shoreline.
- Use of hand broadcast or narrow baiting by helicopter or UAVs for aerial broadcast for applications adjacent to waterbodies, where feasible.
- Limit aerial and most ground broadcast applications to the dry season, reducing offsite runoff to waterbodies.
- Restrict aerial broadcast applications to when wind speeds are below 35 mph, reducing the likelihood of off-site deposition of pellets.
- Cover wells and water tanks during aerial broadcast applications.
- Hand broadcast applications, bait stations, bait trays, and bait sachets can be used adjacent to wells and water tanks.

The above mitigation measures in addition to other label restrictions for brodifacoum formulations are designed to reduce the probability of brodifacoum transport to aquatic areas from drift and runoff. Incidental deposition of brodifacoum into water resources may occur through drift or runoff

from broadcast applications; however, the expected levels in waterbodies and the surrounding ocean would be negligible (Fisher et al. 2010).

Any brodifacoum that would enter the water will do so as a pellet or block that would become saturated and sink to the bottom sediment where it would rapidly degrade. Pellet baits have been shown to degrade in water within minutes to less than five hours in previous eradication efforts (Empson and Miskelly 1999, Howald et al. 2009, Samaniego-Herrera et al. 2014). Additionally, any pellets that are discharged into the ocean side of an island would degrade even more rapidly through the mechanical forces of wave action.

Direct exposure to fish that may consume pellets that incidentally enter aquatic systems appears to be species dependent. Howald et al. (2009) also reported that bait pellets were not consumed by fish or aquatic invertebrates after rodenticide applications on Anacapa Island. However, other studies have shown that fish will consume bait pellets. USFWS (2019) reported that bait material or a pyranine biomarker were observed in specimens of pinktail triggerfish (*Melichthys vidua*), black triggerfish (*Melichthys niger*), stocky hawkfish (*Cirrhitis pinnulatus*), and blue-lined snapper (*Lutjanus kasmira*) immediately after brodifacoum applications. No evidence of bait consumption was found in blacktail snapper (*Lutjanus fulvus*) or blotcheye soldierfish (*Myripristis berndti*). Empson and Miskelly (1999) reported that three species of fish were seen eating non-toxic bait within 15 minutes of entering the marine environment in a rodent eradication project on Kapiti Island. Bait consumption by marine fish would be short-term due to the rapid degradation of pellets once they enter water.

Brodifacoum has low water solubility, 0.24 mg/L at a pH of 7.4, and environmental fate properties that suggest that residues in water would bind to suspended solids and sediment. Its low solubility and high binding affinity for soil also reduce the likelihood of leaching into groundwater resources. Studies of Talon possum bait (0.02 g/kg brodifacoum) exposed to simulated rainfall showed that significant amounts of brodifacoum are unlikely to leach into soil (Booth et al. 1999). A study of anticoagulant leaching on Hawaiian islands showed that brodifacoum had a low leaching potential across forested areas (D'Alessio et al. 2018). The environmental fate properties of brodifacoum will reduce the probability of exposure to vertebrates and invertebrates that occupy the water column. Aquatic exposures would be greatest for aquatic biota that occupy the sediment or would consume benthic prey items.

Secondary exposure to brodifacoum may occur for marine fish species that feed near shore. Masuda et al. (2015) evaluated 11 previous accounts of residue examination of coastal marine species following aerial applications of brodifacoum bait and found the overall rate of residue detection was 3.1% for fish (2 of 65 samples tested) and 5.6% for marine invertebrates (11 of 196 samples tested). The risk to marine fish from secondary exposure to brodifacoum is low based on the low frequency of detection in potential prey items. The exposure to marine fish from secondary exposure will decrease over time as brodifacoum is metabolized and degraded in the marine environment.

#### **4.2.2 Terrestrial Exposure Assessment**

Brodifacoum residues in terrestrial wildlife can occur from primary and secondary oral exposures. Terrestrial invertebrates and vertebrates may be directly exposed to brodifacoum from consuming the bait pellets or ingestion of soil and water that contains brodifacoum residues. Secondary exposure will occur when nontarget terrestrial vertebrates consume invertebrate and vertebrate prey items that contain residues of brodifacoum. These exposures can be both short- and long-term. A majority of the WS use of brodifacoum is for island conservation eradication projects. Compared to other registered uses of brodifacoum, the use pattern is shorter in duration since the eradication project is set for a specific time interval when making broadcast applications over

large areas. There may be some post-eradication treatment exposure due to a need to mop up any remaining rodents that were not eradicated during the primary eradication effort. These applications are typically much smaller in scale and directed when compared to the primary application. Inhalation and dermal exposure to brodifacoum are not anticipated to be a significant exposure pathway for nontarget wildlife. The use of a bait pellet in the APHIS brodifacoum formulations and bait block in the Talon Weatherblok XT formulation and the low potential for brodifacoum to volatilize suggests a low potential for inhalation and dermal exposures.

### *Primary Exposure*

Primary or direct exposure will be greatest for nontarget animals that consume the bait. Dyes have been added to some brodifacoum bait formulations to reduce primary exposure to nontarget birds. Blue and green dyes added to pellets have been shown to deter or reduce bird consumption, reducing the risk of rodenticide exposure (Marples et al. 1998, Hartley et al. 1999, Hartley et al. 2000, Weser and Ross 2013). For bait that are attractive to nontarget animals, the duration of direct exposure will depend on how long bait is available for consumption. In some cases, baits not removed by the target rodent species and any nontarget species will be recovered, but this will vary based on the feasibility of collecting unrecovered baits. Any unrecoverable baits left in the environment from WS use will slowly degrade. Brodifacoum has a half-life of 157 days in sandy clay loam soil incubated in the dark at 21°C (USEPA 1998). It is stable to hydrolysis (USEPA 1998). On Little Barrier Island in New Zealand, brodifacoum bait pellets in exclusion cages were nearly completely disintegrated by day 100 after application (Fisher et al. 2010). About 96% of aerially applied brodifacoum pellets had completely broken down by 120 days in open grassed areas; degradation in the forested area was slightly slower (Fisher et al. 2010).

### *Secondary Exposure*

Secondary exposure of brodifacoum to scavenging and predatory birds and mammals have been noted for various species. There is the potential for brodifacoum residues to occur in terrestrial invertebrates that consume brodifacoum pellets or blocks and then be exposed to birds and mammals that consume invertebrates (Howald et al. 2009). Walther et al. (2021) noted brodifacoum residues in three insectivorous bird species that frequent farms where brodifacoum use was reported. Within the sampled birds, the Great tit, *Parus major*, European robin, *Erithacus rubecula*, and Dunnock, *Prunella modularis*, had brodifacoum liver tissue residues of 23.3, 44.4, and 40.9%, respectively. Residue levels and frequency decreased the further the collection distance from fields where brodifacoum had been used.

Herring et al. (2022) reported brodifacoum exposure in the turkey vulture and the federally listed California condor. In the turkey vulture, 80% of plasma samples showed detectable levels of brodifacoum, while in the California condor, 56% of liver samples showed detectable levels of brodifacoum. Niedringhaus et al. (2021) reported that anticoagulant rodenticide exposure in bald eagles (*Haliaeetus leucocephalus*) and golden eagles (*Aquila chrysaetos*) was 83% and 77%, respectively, when measuring residues in the liver. Brodifacoum was the most frequently detected anticoagulant rodenticide at 81%. Brodifacoum secondary exposure has also been observed in other predatory and scavenging bird species, such as owls (Wiens et al. 2019, Hofstadter et al. 2021) and hawks (Murray 2017;2020, Hopf-Dennis et al. 2022), and in one passerine species, the Stewart Island robin (*Petroica australis rakiura*) (Masuda et al. 2014). The secondary exposure noted in the passerine species is from nestlings consuming invertebrate prey that the adults bring to the nestlings.

Musto et al. (2024) reported that 61.8% of samples collected from grey wolves (*Canis lupus*) had detectable levels of anticoagulant rodenticides with brodifacoum being the most common. Secondary mammal exposure to brodifacoum has also been noted in the Eurasian river otter, *Lutra lutra*. Regnery et al. (2024) reported liver brodifacoum residues ranging from 11% to 81.1% in Eurasian river otters sampled from various German federal states. Otters are piscivorous predators with secondary exposure from consuming contaminated fish prey. Murphy et al. (1998) reported a 78%, 71%, and 56% incidence of brodifacoum residues in the livers of stoats (*Mustela erminea*), weasels (*M. nivalis*), and ferrets (*M. furo*), respectively, after a large-scale eradication of invasive rats and opossums in a New Zealand forest habitat.

Brodifacoum has also been observed in reptiles, specifically snake and lizard species. Lettoof et al. (2020) reported brodifacoum residues in the livers of a rodent predator snake species, a frog predator snake species, and an omnivorous lizard. Sample sizes were low, however brodifacoum was the most detected anticoagulant rodenticide.

Primary and secondary exposure to any terrestrial vertebrate is of concern. Brodifacoum exposure to birds is of particular concern as islands serve as breeding and overwintering sites for many seabirds and shorebirds. WS working with its cooperators on island conservation projects have implemented several mitigation measures to reduce disturbance and exposure to birds from brodifacoum applications for island conservation projects. Below is a list of measures that may be used to reduce disturbance and minimize primary and secondary brodifacoum exposures to birds and mammals:

- Select the color and size of the rodenticide baits to minimize attractiveness of the bait to birds.
- Use UAVs in areas of high bird activity to reduce disturbance and the probability of bird strikes.
- Remove animal carcasses that could potentially be a source of secondary poisoning for analysis or incineration.
- Use special measures, such as hand broadcast applications or the use of deflector shield, directional spreader, or trickle bucket for aerial applications, to prevent bait from entering the water and contaminating food sources that are bird and mammal prey items.
- Conduct broadcast applications when seasonal bird activities, including nesting, are minimal.

The use of the above mitigation measures to reduce brodifacoum exposure to birds and mammals is site specific. For example, the removal of carcasses may not be feasible if they are in unsafe or inaccessible areas or collecting the large numbers of dead rodents may be impractical.

## **5 RISK CHARACTERIZATION**

This section discusses the qualitative risks associated with the proposed use of brodifacoum. The evaluation of documented brodifacoum health exposure data and relevant animal exposure studies applied to exposure assumption scenarios can quantify the risk of impact to human health and nontarget fish and wildlife if accidentally exposed. Deterministic methods are used, where appropriate, to determine if expected environmental residues exceed toxicity data suggesting possible risk. In other cases, a qualitative discussion regarding risk may rely on literature and additional information to further elaborate on the potential for injury or harm.

## **5.1 Human Health**

Risks associated with adverse human health are characterized qualitatively for this section. Occupational risk for applicators was not quantified due to the lack of a relevant toxicity endpoint to estimate a hazard quotient (HQ). Dermal and inhalation exposures were identified as a potential exposure pathway; however, sublethal and/or long-term inhalation and dermal toxicity data was not available for either pathway. Sublethal and chronic toxicity data is available for oral exposures; however, this exposure pathway is not relevant for estimating inhalation and dermal risks to applicators.

Occupational risks for applicators are anticipated to be low due to the lack of dietary exposure and label requirements regarding PPE when loading, applying, or handling products containing brodifacoum. PPE requirements will minimize inhalation and dermal risks to applicators.

Brodifacoum risks to the public from island conservation uses are low. To date no adverse effects to human health have been reported when using brodifacoum as a rodenticide in island conservation projects. Castaño et al. (2023) reviewed data from 153 island rodent eradication projects, many of which used brodifacoum as the primary rodenticide. There were no reports of adverse effects to the public or workers from oral, dermal, or inhalation exposures, or secondary or tertiary exposures.

The low risk to the public is due to the label restrictions and additional mitigation measures (see Section 4.1.1) including those on the supplemental labels which have higher broadcast use rates (USEPA 2019a;b). For many sites that have been treated in past eradication efforts the public is not allowed on the island or there is no permanent habitation. In situations where the public may be present, the label restrictions and other mitigation measures reduce the risk to the public. Finally, brodifacoum is not registered for use on food crops, and other dietary resources such as drinking water are at low risk from contamination due to label restrictions, additional mitigation measures (see Section 4.2.1), and its environmental fate. Similarly, the risk to the public from WS use of Talon Weatherblok XT is low due to label restrictions and WS use patterns.

## **5.2 Ecological Risks**

Risk characterization combines information from the dose-response assessment with the exposure assessment to determine the potential adverse effects on aquatic and terrestrial species. In this risk assessment, WS uses USEPA's risk evaluations (USEPA 2016c;2020b), peer-reviewed scientific literature, product labels, and WS use patterns to characterize the risks associated with WS applications of brodifacoum bait.

### **5.2.1 Aquatic**

Acute and chronic risks to aquatic vertebrates and invertebrates are anticipated to be low for most brodifacoum uses. Aerial broadcast applications pose the greatest risk to nontarget aquatic organisms; however, as discussed in section 4.2.1, WS uses additional measures to reduce the likelihood of brodifacoum residues entering waterbodies and the surrounding marine environment. Nontarget aquatic risk would be greatest for small, isolated waterbodies occurring on an island. Shallow lagoon areas on the perimeter of the island could also pose a risk to aquatic organisms; however, tidal effects, brodifacoum's environmental fate, and dilution will reduce the risks.

Furthermore, any brodifacoum-containing rodenticide pellets or blocks that enter the marine environment will become saturated and break down rapidly, with remaining brodifacoum residues being diluted and partitioning to suspended solids and sediment, where the brodifacoum will

slowly degrade, resulting in low risk to marine invertebrates. USFWS (2019) reported no impacts to coral species associated with the rat eradication project on Palmyra Atoll. Caliani et al. (2023) sampled several fish species 10 days after a rodent eradication project on Tavolara Island, an Italian Marine Protected Area. Results from the study showed no brodifacoum residues in fish and no effect on various biomarkers suggesting no sublethal impacts.

Brodifacoum concentrations at which adverse effects have been reported would not occur under any realistic exposure scenario using typical use patterns. For example, if one pound of bait were dissolved into a 10'x10'x1' or any 100 ft<sup>2</sup> area of ocean, it would result in about 0.004 mg/L in that area (this is not likely to happen as discussed because it is more likely to bind to sediment and soil). This resulting concentration is insufficient to result in adverse effects to aquatic organisms based on available toxicity data. Anticipated brodifacoum risks to the marine environment will be very low based on label requirements for treatment and additional mitigation measures used by WS to protect marine environments.

Howald et al. (2009) also reported that bait pellets were not consumed by fish or aquatic invertebrates after rodenticide applications on Anacapa Island. However, other studies have shown that fish will consume bait pellets. USFWS (2019) reported that bait material or a pyranine biomarker were observed in specimens of pinktail triggerfish (*Melichthys vidua*), black triggerfish (*Melichthys niger*), stocky hawkfish (*Cirrhitis pinnulatus*), and blue-lined snapper (*Lutjanus kasmira*) immediately after brodifacoum applications. No evidence of bait consumption was found in blacktail snapper (*Lutjanus fulvus*) or blotcheye soldierfish (*Myripristis berndti*). Empson and Miskelly (1999) reported that three species of fish were seen eating non-toxic bait within 15 minutes of entering the marine environment in a rodent eradication project on Kapiti Island. Bait consumption by marine fish appears to be species dependent and based on the availability of the pellet, which is short-term. Brodifacoum-containing pellets that enter the marine environment break down rapidly with remaining brodifacoum residues being diluted and partitioning to suspended solids and sediment, where brodifacoum will slowly degrade. The amount of brodifacoum that could enter the marine environment is expected to be very low from the proposed applications based on the application sites and mitigation measures designed to protect aquatic resources. Risks to marine fish species from brodifacoum residues in water or sediment is expected to be negligible.

Brodifacoum residues could potentially accumulate in marine invertebrates and pose a chronic risk. Masuda et al. (2015) evaluated eleven previous accounts of residue examination of coastal marine species following aerial applications of brodifacoum bait and found the overall rate of residue detection was 5.6% for marine invertebrates (11 of 196 samples tested). The sublethal and chronic effects from these types of exposures to marine invertebrates is unknown; however, the frequency of detection is low, suggesting no population level effects to marine invertebrates. The low incidence of brodifacoum residues would suggest secondary risks to aquatic organisms that consume marine invertebrates would also be low.

The exposure to aquatic invertebrates would be higher for sediment dwelling invertebrates due to the chemical and environmental fate characteristics of brodifacoum. Brodifacoum toxicity to benthic invertebrates is expected to be comparable based on available freshwater invertebrate toxicity data. The risks to benthic invertebrates are likely low due to the reduced bioavailability that may occur as brodifacoum binds tightly to soil and sediment (USEPA 2020b). Any impacts to sediment-dwelling invertebrates would be short- or long-term due to the persistence of brodifacoum.

Marine mammals, sea turtles, and offshore fish species are anticipated to have negligible risk of adverse impacts from any incidental brodifacoum transport to sea water. Dilution, the physical

wave action to break up pellets, and the environmental fate of brodifacoum would not result in detectable levels of brodifacoum where those species would be expected to forage.

Based on the lack of aquatic exposure, label restrictions, and WS use pattern, APHIS considers the risk to aquatic species as negligible for island conservation uses. Brodifacoum risks to aquatic nontarget species would be even less under non-island conservation uses. Non-island conservation uses are restricted to near structure applications with lower use rates and more restrictive application methods than those used for island conservation. Additionally, WS personnel use is negligible for non-island applications.

### 5.2.2 Terrestrial

Brodifacoum toxicity and exposure can result in acute and chronic primary and secondary risks to most terrestrial vertebrates. Direct ingestion of bait by nontarget terrestrial wildlife would be expected to result in adverse acute and chronic effects dependent on the dose received and duration of exposure.

USEPA (2020b) conducted a screening level risk assessment to evaluate the direct risk to birds, reptiles, and mammals from brodifacoum exposure across multiple body weights and food intake values. In the absence of standardized toxicity data for reptiles, USEPA uses bird toxicity data to estimate acute risks. The exposure estimates were divided by acute toxicity values that were adjusted for body weights to calculate a risk quotient (RQ) (Table 6). USEPA uses levels of concern (LOC) to determine if there is a risk to a group of animals by comparing the RQ to the LOC. In the case of terrestrial vertebrate wildlife USEPA uses a LOC of 0.5. An RQ above 0.5 suggests an acute high risk to nontarget vertebrates. USEPA also uses an LOC of 0.1 for determining risk to federally threatened and endangered species. A RQ was estimated for different body weight categories of birds and mammals (Table 6).

Table 6. Estimated acute risk quotient (RQ) values for brodifacoum (25 ai-mg/kg bait) in birds and mammals.

| Class             | Weight (g) | Adjusted LD <sub>50</sub> (mg ai/kg-bw <sup>1</sup> ) | Brodifacoum intake <sup>2</sup> (mg ai/kg-bw) | RQ <sup>3</sup> | Brodifacoum body burden <sup>4</sup> (mg ai/kg-bw) | RQ <sup>3</sup> |
|-------------------|------------|-------------------------------------------------------|-----------------------------------------------|-----------------|----------------------------------------------------|-----------------|
| Passeriform Birds | 20         | 185.9                                                 | 6.35                                          | 0.03            | 76                                                 | <b>117</b>      |
| Passeriform Birds | 100        | 236.6                                                 | 4.99                                          | 0.02            | 60                                                 | <b>135</b>      |
| Passeriform Birds | 1000       | 334.2                                                 | 3.53                                          | 0.01            | 42                                                 | <b>166</b>      |
| Rodent Mammals    | 15         | 5.5                                                   | 4.77                                          | <b>0.87</b>     | 57                                                 | <b>59</b>       |
| Rodent Mammals    | 35         | 4.4                                                   | 3.29                                          | <b>0.75</b>     | 39                                                 | <b>51</b>       |
| Rodent Mammals    | 1000       | 1.9                                                   | 0.76                                          | 0.40            | 9                                                  | <b>27</b>       |

<sup>1</sup> mg ai/kg-bw = milligrams active ingredient per kilogram body weight

<sup>2</sup> Single day of bait exposure

<sup>3</sup> Risk quotients in bold exceed the acute high-risk LOC of 0.5.

<sup>4</sup> Six consecutive days of bait exposure

Reference: (USEPA 2020b)

The acute high-risk LOC was exceeded for 15g and 35g body weights for mammals in single- and six-day exposures. The acute high-risk LOC was not exceeded for any of the three avian body weights from a single day exposure, however all LOCs were exceeded when assuming six consecutive days of bait exposure. These estimates are screening values that allow risk assessors to identify taxa groups requiring additional risk evaluation. The endpoint used to derive the effect value is an LD<sub>50</sub> which is based on mortality. Sublethal impacts may also occur at lower doses and those risks are not estimated in Table 6. These risks will be reduced as the bait is

removed by the target pest and nontarget species, and as the bait pellet and brodifacoum degrade in the environment.

Primary and secondary risks of brodifacoum to nontarget mammals and birds will vary based on their food preferences. USFWS evaluated the primary and secondary acute risk to seabirds and shorebirds on Sand Island at Midway Atoll from Brodifacoum-25W Conservation applications (USFWS 2019) (Table 7). USFWS estimated the acute poisoning risk to seabirds and shorebirds using acute lethality data and estimating food intake values. Estimates of acute risk from direct ingestion of pellets or ingesting prey containing brodifacoum were made by estimating the percentage of daily food needed to receive a lethal dose of brodifacoum. USFWS categorized the primary and secondary poisoning risk from brodifacoum exposure using toxicity estimates and feeding habits for seabirds and shorebirds.

Generally, primary and secondary risks of brodifacoum exposure to seabirds is lower due to their feeding habits that consists mostly of marine prey items. For example, the sooty tern, a common nesting seabird, has a low risk of primary and secondary exposure to brodifacoum based on their diet. Sztukowski and Kelser (2012) demonstrated that sooty tern chicks on Wake Atoll did not preferentially consume placebo bait pellets, also suggesting a low risk of brodifacoum risk to sooty tern chicks.

Secondary poisoning risks to birds are short- and long-term; however, brodifacoum residues in bird prey items such as invertebrates, lizards, and marine fish will decline over time. Wegmann et al. (2019) reported no brodifacoum residues in mullet (*Moolgarda engeli*), cockroaches (*Periplaneta* sp.), geckos (*Lepidodactylus lugubris*), hermit crabs (*Coenobita perlatus*), and fiddler crabs (*U. tetragonon*) three years post-eradication on Palmyra Atoll. Siers et al. (2020) reported no brodifacoum residues in fish samples collected within the lagoon at Wake Atoll, or within near-shore waters outside the lagoon three years after the 2012 eradication. Traces of brodifacoum were detected in 2 out of 20 blacktail snapper (*Lutjanus fulvus*) fish samples that were collected in an intermittent land-locked pond in an area that received significant brodifacoum baiting. Although at levels too low to quantify, the study demonstrated that brodifacoum can persist in aquatic environments, especially smaller isolated water bodies.

Table 7. Risk summary for seabirds and shorebirds exposed to brodifacoum from rat eradication activities\*.

| Species                                                  | Primary Poisoning Risk | Secondary Poisoning Risk |
|----------------------------------------------------------|------------------------|--------------------------|
| Laysan Albatross, <i>Phoebastria immutabilis</i> (adult) | Low                    | Low                      |
| Black-footed Albatross, <i>P. nigripes</i>               | Low                    | Low                      |
| Albatross (chicks all spp.)                              | Low                    | Low                      |
| Wedge-tailed shearwater, <i>Ardenna pacifica</i>         | Low                    | Low                      |
| Christmas shearwater, <i>Puffinus nativitatis</i>        | Low                    | Low                      |
| Great frigatebird, <i>Fregata minor</i>                  | Low                    | Medium                   |
| White-tailed tropicbird, <i>Phaethon lepturus</i>        | Low                    | Low                      |
| Red-tailed tropicbird, <i>P. rubricauda</i>              | Low                    | Low                      |
| Masked booby, <i>Sula dactylatra</i>                     | Low                    | Low                      |
| Brown booby, <i>S. leucogaster</i>                       | Low                    | Low                      |
| Red-footed booby, <i>S. sula</i>                         | Low                    | Low                      |
| Black noddy, <i>Anous minutus</i>                        | Low                    | Low                      |
| Brown noddy, <i>A. stolidus</i>                          | Low                    | Low                      |

| Species                                             | Primary Poisoning Risk | Secondary Poisoning Risk |
|-----------------------------------------------------|------------------------|--------------------------|
| White tern, <i>Gygis alba</i>                       | Low                    | Medium                   |
| Sooty tern, <i>Onychoprion fuscatus</i>             | Low                    | Low                      |
| Gray-backed tern, <i>O. lunatus</i>                 | Low                    | Low                      |
| Pacific golden plover, <i>Pluvialis fulva</i>       | High                   | High                     |
| Ruddy turnstone, <i>Arenaria interpres</i>          | High                   | High                     |
| Wandering tattler, <i>Tringa incana</i>             | High                   | High                     |
| Gray-tailed tattler, <i>T. brevipes</i>             | High                   | High                     |
| Sanderling, <i>Calidris alba</i>                    | High                   | High                     |
| Dunlin, <i>C. alpina</i>                            | High                   | High                     |
| Sharp-tailed sandpiper, <i>C. acuminata</i>         | High                   | High                     |
| Bristle-thighed curlew, <i>Numenius tahitiensis</i> | High                   | High                     |

\*(USFWS 2019)

Birds that consume bait or prey contaminated with bait are at short- and long-term risk from brodifacoum. Short-term primary risk is greatest immediately after treatment and will decline as bait is removed by the target rodents, some nontarget species, and as the pellets degrade in the environment. Aerial broadcast applications pose the greatest risk to nontarget species since they are typically broadcast over a larger area. Aerial applications typically occur within an approximate 30-day window with 2 to 3 applications during that time under the current supplemental labels. The FIFRA Section 3 label for Brodifacoum-25D Conservation and Brodifacoum-25W Conservation allow only 1 to 2 aerial broadcast applications with a 5 to 7-day interval between applications. Mitigation measures for nontarget terrestrial vertebrates that were summarized in Section 4.2.2 reduce the potential for short- and long-term primary and secondary risks.

Hand baiting using bait bolas, burrow baiting, floating bait stations, and tamper-proof baiting stations can be used over a longer period for eradication and control efforts. These application methods can result in a short- and long-term risk; however, these methods of application are typically used for smaller areas of treatment compared to aerial broadcast applications. Bait removal by the target rodent species will reduce long term primary risks to nontarget animals that may also consume bait. In some cases, for aerial and ground applications, rodents may be collected after application, thus reducing short- and long-term secondary risks to nontarget animals. As previously stated, the level of carcass removal will vary depending on site conditions. For example, collection and disposal may not be feasible if treatments occur in an area where there are high natural mortality rates for nontarget species such as bird breeding areas. Label requirements for collection and disposal of spilled bait also reduce primary and secondary risks.

Brodifacoum primary and secondary risks to nontarget wildlife have been noted under past use. USEPA (2020b) reported that second generation anticoagulant rodenticides (SGARs) resulted in adverse incident reports for more than 70 species of birds and 30 species of mammals. Brodifacoum was linked to approximately 60% of the SGAR incident reports for birds and 43% of the incident reports in mammals. Brodifacoum primary and secondary risks to birds have been identified in large scale aerial rodent eradication programs. Ebbert and Burek-Huntington (2010) reported more than 420 bird carcasses were collected after an eradication program to remove the Norway rat from Rat Island, Alaska using Brodifacoum-25W Conservation. Approximately 24 species of birds were collected with glaucous-winged gulls (*Larus glaucescens*) and bald eagles (*Haliaeetus leucocephalus*) being the most collected. Of the seventy birds necropsied almost all showed signs of brodifacoum exposure, including extensive hemorrhaging. Brodifacoum

exposure continued at Rat Island for at least nine months after application demonstrating acute and chronic risks.

There is a low risk to terrestrial invertebrates that are exposed to brodifacoum pellets and blocks. Spurr and Drew (1999) reported that terrestrial invertebrates like crickets, beetles, and ants are attracted to cereal baits used in rat eradication programs in New Zealand. Terrestrial invertebrates may also scavenge dead rats that have been exposed to brodifacoum. Based on available toxicity data, the risk to this group of nontarget species is expected to be low. Effects data are limited for terrestrial invertebrates, but earthworm, snail and crab exposures show low toxicity after exposure to high concentrations of brodifacoum in laboratory toxicity testing (Booth et al. 2003). Pain et al. (2000) also demonstrated low brodifacoum toxicity to the hare-lipped land crab (*Johngarthia (Gecarcinus) lagostoma*). However, on Palmyra Atoll, some fiddler crabs (*U. tetragonon*) may have died from brodifacoum poisoning in conjunction with the rat eradication (Pitt et al. 2015). Applications on Palmyra Atoll were higher than those that have been used on other island conservation projects. USEPA (2020b) pesticide incident reporting suggests a low number of crab mortalities associated with SGAR use. Any impacts to terrestrial invertebrate populations would be expected to be short duration. Bait pellet removal by the target pest and other nontarget species, and brodifacoum degradation would allow invertebrate populations to recover.

There is the potential for brodifacoum residues to occur in terrestrial invertebrates that consume brodifacoum pellets or blocks (Howald et al. 2009). The sublethal impacts of these residues to terrestrial invertebrates is unknown but population increases of crabs and other invertebrate populations post-eradication suggest that the impacts are minimal and transient. The presence of brodifacoum residues in terrestrial invertebrates does pose a secondary risk for those nontarget species that rely on terrestrial invertebrates as a food source.

Brodifacoum binds to soil and is not considered systemic in plants (WHO 1995). However, in a recent study dosing soil with brodifacoum at 100 g/m<sup>2</sup> or 500 g/m<sup>2</sup> resulted in residues in wheat ranging from 0.012 mg/kg to 0.0436 mg/kg (Miño et al. 2019). For the study, bait pellets were incorporated into the soil and allowed to degrade releasing brodifacoum into the soil. The removal of bait by the target rodent species and other nontarget species suggests that long term exposure of plants to brodifacoum in soil is unlikely. The use of a weather-resistant pellet formulations, removal of pellets by the target species and other nontarget animals, and the anticoagulant mode of action of brodifacoum suggests no direct risks to terrestrial plants.

APHIS recognizes the primary and secondary risks associated with brodifacoum use in island conservation projects. Mitigation measures to reduce terrestrial and aquatic exposure reduce these risks but do not eliminate them. Castaño et al. (2021) identified three strategies that can be used to reduce nontarget risk from rodenticide use in invasive rodent eradication programs on islands. Strategies include exposure avoidance, risk minimization, and remediation with several tactics identified within each strategy. Some of these measures are already components of island eradication efforts using brodifacoum. The use of other strategies in future island conservation projects will be dependent upon site specific conditions.

The use of brodifacoum and other rodenticides as a tool in island conservation has been shown to provide beneficial impacts to native flora and fauna post eradication (Thibault 1995, Jouventin et al. 2003, Harper and Bunbury 2015, Newton et al. 2016, Graham et al. 2018, Wolf et al. 2018, Herrera-Giraldo et al. 2019, USFWS 2019). The primary and secondary adverse risks to nontarget fish and wildlife from brodifacoum applications can be offset by the positive impacts invasive rodent eradication and control can have on endemic island species post eradication.

Brodifacoum risks to terrestrial nontarget species are considered much lower for non-island conservation uses when compared to island uses. Non-island conservation uses are restricted to near structure applications (i.e. no applications beyond 100 feet of a structure) with lower use rates, no broadcast applications, and more restrictive application methods than those used for island conservation purposes. Additionally, WS personnel use is negligible for these types of applications.

## **6 UNCERTAINTIES AND CUMULATIVE IMPACTS**

The uncertainties associated with this risk evaluation arise primarily from the limited toxicity information available for the various brodifacoum formulations. Unpublished acute toxicology studies submitted to USEPA by registrants and individual formulation safety data sheets provide limited acute mammalian toxicity values, which are then used to make general conclusions concerning the impact of brodifacoum on humans and the non-target environment.

Other uncertainties related to chronic and sublethal effects data for some fish and wildlife and surrogacy of test organisms are typical for most pesticides; however, there is a considerable amount of field data related to poisoning of nontarget wildlife with anticoagulant rodenticides. This information provides a weight-of-evidence approach to conservatively evaluate the risk of brodifacoum to nontarget organisms. The conservative assumptions regarding the potential for exposure to human health, nontarget species, and the environment address the uncertainties to some extent. A lack of risk using these conservative assumptions supports the reasonable certainty that impacts on human health and the environment will be negligible. However, primary, and secondary risks to nontarget mammals are not negligible, particularly for broadcast applications.

Another area of potential uncertainty in this risk assessment is the potential for cumulative impacts on human health, nontarget species, and the environment from the proposed use of brodifacoum by WS. Areas where cumulative impacts could occur are: 1) repeated worker and environmental exposures to brodifacoum from program application; 2) co-exposure to other chemicals with a similar mode of action; and 3) exposures to other chemicals affecting the toxicity of brodifacoum.

Repeated exposures that increase risk of injury from accidental brodifacoum exposure by WS applications are expected to be minimal due to strict WS applicator adherence to label-required PPE. Additionally, the labels limit the application frequency, the maximum amount allowed during each application, and the total amount allowed overall.

## **7 PREPARERS: WRITERS, EDITORS, AND REVIEWERS**

### **7.1 APHIS WS Methods Risk Assessment Committee**

#### **Writers for “Use of Brodifacoum in Wildlife Damage Management Risk Assessment”:**

**Writer:** Jim Warren

**Position:** USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Environmental Toxicologist, Little Rock, AR

**Education:** B.S. Forest Ecology and M.S. Entomology – University of Missouri; Ph.D. Environmental Toxicology – Clemson University

**Experience:** Eighteen years of experience working for APHIS preparing ecological risk assessments and providing environmental compliance support. Prior experience before joining APHIS includes other government and private sector work regarding ecological risk assessments related to various environmental regulations.

**Writer:** Andrea Lemay

**Position:** USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Biological Scientist, Raleigh, NC

**Education:** BS Plant and Soil Science (Biotechnology) - University of Massachusetts; MS Plant Pathology - North Carolina State University

**Experience:** Thirteen years of service in APHIS conducting risk analysis. Nine years of experience in preparing environmental analyses in compliance with the National Environmental Policy Act.

#### **Editors/Contributors for “Use of Brodifacoum in Wildlife Damage Management Risk Assessment”:**

**Editor:** Shelagh DeLiberto

**Position:** USDA-APHIS-Wildlife Services (WS), National Wildlife Research Center (NWRC), Wildlife Biologist, Fort Collins, CO

**Education:** BA Biology and Environmental Science – Ithaca College; MS Wildlife Biology – Colorado State University

**Experience:** Twenty years of service in APHIS conducting wildlife research. Four years of experience preparing categorical exclusions and environmental analyses in compliance with the National Environmental Policy Act.

**Editor:** Emily Ruell

**Position:** USDA-APHIS-WS, NWRC, Registration Manager, Fort Collins, CO

**Education:** B.S. Zoology and Biological Aspects of Conservation – University of Wisconsin - Madison; M.S. Ecology – Colorado State University (CSU); M.A. Political Science – CSU

**Experience:** Nine years of experience with APHIS WS NWRC preparing and reviewing vertebrate pesticide registration data submissions and other registration materials, and providing pesticide regulatory guidance to WS, WS NWRC, and collaborators. Prior experience before joining APHIS includes seven years of conducting field and laboratory wildlife research at CSU, and environmental policy research for the U.S. Geological Survey.

**Contributor:** Thomas C. Hall

**Position:** USDA-APHIS-WS, Operational Support Staff, Staff Wildlife Biologist, Fort Collins, CO

**Education:** BS Biology (Natural History) and BA Psychology – Fort Lewis College; MS Wildlife Ecology – Oklahoma State University

**Experience:** Special expertise in wildlife biology, identification, ecology, and damage management. Thirty-seven years of service in APHIS Wildlife Services including operations and research in CO for research and OR, GU, CA, OK, and NV for operations conducting a wide variety of programs including bird damage research and management, livestock protection, invasive species management, wildlife hazard management at airports, property and natural resource protection including waterfowl, brown tree snake, feral swine, rodent, and beaver damage management. Applied and supervised chlorophacinone use.

## 7.2 Internal Reviewers

### USDA APHIS Wildlife Services

**Reviewer:** Sarah K. Hibbs-Shipp, PhD

**Position:** Regulatory Support Services Unit Leader (Technology Transfer Manager)

**Education:** BA Biology – Grinnell College, Grinnell, IA; MS & PhD Nutrition Science – Colorado State University, Fort Collins, CO.

**Experience:** One year of regulatory review experience with the National Wildlife Research Center, providing guidance and editorial review for pesticide and other briefing content. Prior to joining the USDA, five years of technology transfer/product development work with Colorado State University, which included developing/authoring and reviewing lay public oriented science communication briefs and non-confidential technology summaries. Previous to CSU, thirteen years of clinical research and development study management for Phase I-IV dermatology-focused and other non-life-threatening drug development regulated research submitted to the FDA, as well as extensive safety, efficacy, and claim substantiation research for inclusion in FTC review packages prior to marketing implementation.

**Reviewer:** Rickey L. Gilliland

**Position:** District Supervisor Wildlife Biologist USDA-APHIS-WS

**Education:** BS Oklahoma State University – Wildlife Ecology

**Experience:** 34 years of field and supervisory experience which includes field rodent control and disease research (Texas Wildlife Services Program)

## 7.3 Peer Review

The Office of Management and Budget requires agencies to have peer review guidelines for scientific documents. The APHIS guidelines were followed to have "Minimum Risk Pesticides" peer reviewed. WS worked with the Association of Fish and Wildlife Agencies to have experts review the documents.

### 7.3.1 Peer Reviewers Selected by the Association of Fish and Wildlife Agencies

Texas Parks and Wildlife Department

Louisiana Department of Wildlife and Fisheries

Division of Fish and Wildlife, Department of Planning and Natural Resources, Government of the Virgin Islands

### 7.3.2 Comments

1. Page 11: “3) migration potential to groundwater and surface water” The explanation I see is: “Brodifacoum has a low migration potential to groundwater and surface water (USEPA 2016c)” .

I think this can be expanded upon or further explained to help the reader understand why that is the case. Also mentioning environmental fate with 25D if it were to rain soon after deployment, which is a possibility, I imagine.

**Response:** In Section 4.2.1 we further explain the environmental fate of brodifacoum beyond the statement in Section 2.2. Section 4.2.1 states “Brodifacoum has low water solubility, 0.24 mg/L at a pH of 7.4, and environmental fate properties that suggest that residues in water would bind to suspended solids and sediment. Its low solubility and high binding affinity for soil also reduce the likelihood of leaching into groundwater resources.”

We have added information in Section 4.2.1 describing studies evaluating the environmental fate of brodifacoum due to rain events and the potential for leaching.

2. I missed the environmental fate of brodifacoum if the target animals are left on site to decompose. It is mentioned that the half-life in soil is 157 days, and that it binds to organic matter, but missing what the fate of brodifacoum is when left in the environment through a decomposing animal. Half-life in decomposing mammals, birds, fish?

**Response:** We report the half-life of brodifacoum in rat liver (130 days) in Section 2.3.1. We were unable to find any studies that determined the residue of brodifacoum available after an animal was exposed to brodifacoum and decomposed on the landscape.

**Responses not requiring a response:**

1. Thank you for the opportunity to review the document. The risk assessment is thorough, and I have no substantive comments.
2. I found the document to be very thorough and it covered every aspect of brodifacoum use that I could think of including human, wild, and domestic animal toxicity parameters. Additionally, there was a myriad of environmental impact information including dilutional translation in aquatic environments which puts aquatic toxicity in a realistic frame-of-view compared to simple aquatic toxicity on organisms in captivity.
3. Overall, a very good piece of information that paints a clear picture of appropriate product use and PPE, as well as expected toxic results and efficacy. Concise information is present pertinent to physical mechanisms for environmental protection in various situations.
4. Useful information on human exposure treatment and half-life of brodifacoum allows the reader good, easily accessible material for use in the event of human exposure and illuminates how potent this toxicant is and how serious human exposure could be.
5. I noticed no technical errors assuming they were not in the baseline data values which I did not research.
6. All references seem to be in order.
7. The risk assessment is thorough, and I have no substantive comments, but thank you for the opportunity to review the document.

## 8 LITERATURE CITED

- Barkman, A. L., and R. H. Richmond. 2022. The effects of brodifacoum cereal bait pellets on early life stages of the rice coral *Montipora capitata*. *PeerJ* 10:e13877.
- Bell Laboratories. 2015a. Brodifacoum 25D Conservation Pellets, Safety Data Sheet.
- \_\_\_\_\_. 2015b. Brodifacoum 25W Conservation Pellets, Safety Data Sheet.
- Booth, L. H., P. Fisher, V. Heppelthwaite, and a. C. T. Eason. 2003. Toxicity and residues of brodifacoum in snails and earthworms. New Zealand Department of Conservation Science Internal Series.
- Booth, L. H., S. C. Ogilvie, and C. T. Eason. 1999. Persistence of sodium monofluoroacetate (1080), pindone, cholecalciferol, and brodifacoum in possum baits under simulated rainfall. *New Zealand Journal of Agricultural Research* 42:107-112.
- Browne, P., R. S. Judson, W. M. Casey, N. C. Kleinstreuer, and R. S. Thomas. 2015. Screening chemicals for estrogen receptor bioactivity using a computational model. *Environmental Science and Technology* 49:8804-8814.
- Caliani, I., A. Di Noi, C. Amico, R. Berni, M. Romi, G. Cai, M. Guarnieri, A. Navone, G. Spano, G. R. Howald, P. Sposimo, and L. Marsili. 2023. Brodifacoum levels and biomarkers in coastal fish species following a Rodent eradication in an Italian marine protected area: Preliminary results. *Life* 13: 415:12 pp.
- Castañó, P. A., K. J. Campbell, G. S. Baxter, V. Carrion, F. Cunninghame, P. Fisher, R. Griffiths, C. C. Hanson, G. R. Howald, W. J. Jolley, B. S. Keitt, P. J. McClelland, J. B. Ponder, D. Rueda, G. Young, C. Sevilla, and N. D. Holmes. 2021. Managing non-target wildlife mortality whilst using rodenticides to eradicate invasive rodents on islands. *ResearchSquare*:28 pp.
- Castañó, P. A., C. C. Hanson, K. J. Campbell, V. Carrión, P. Fisher, E. Ruell, D. Will, and S. Sier. 2023. Invasive rodent eradication on islands: assessment and mitigation of human exposure to rodenticides. *Biological Invasions* 25:653–671.
- D'Alessio, M., T. Wang, C. E. Swift, M. S. Shanmugam, and C. Ray. 2018. A Tier-I leaching risk assessment of three anticoagulant compounds in the forested areas of Hawai'i. *Science of the Total Environment* 630:889-902.
- Driessnack, M. K., L. Pavord, and J. K. McIntyre. 2023. Evaluating the Potential Hazards of Anticoagulant Rodenticides to Early Life Stages of Coho Salmon (*Oncorhynchus kisutch*), Final Report to USDA APHIS. Washington State University, Puyallup Research and Extension Center.
- Ebbert, S., and K. Burek-Huntington. Anticoagulant Residual Concentration and Poisoning in Birds Following a Large-Scale Aerial Application of 25 ppm Brodifacoum Bait for Rat Eradication on Rat Island, Alaska. University of California, Davis, 2010.
- ECHA. 2023. Endocrine disruptor assessment list: queried brodifacoum and bromethalin. European Chemical Agency.
- Empson, R. A., and C. Miskelly. 1999. The risks, costs and benefits of using brodifacoum to eradicate rats from Kapiti Island, New Zealand. *New Zealand Journal of Ecology* 23:241-254.
- EU. 2016. Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products, Evaluation of active substances, Renewal of approval Assessment Report. European Union.
- Fisher, P., R. Griffiths, C. Speedy, and K. Broome. Environmental Monitoring for Brodifacoum Residues after Aerial Application of Baits for Rodent Eradication. University of California, Davis, 2010.
- Flores, F., S. Kaserzon, G. Elisei, G. Ricardo, and A. P. Negri. 2020. Toxicity thresholds of three insecticides and two fungicides to larvae of the coral *Acropora tenuis*. *PeerJ* 8:e9615.
- Graham, N. A. J., S. K. Wilson, P. Carr, A. S. Hoey, S. Jennings, and M. A. MacNeil. 2018. Seabirds enhance coral reef productivity and functioning in the absence of invasive rats. *Nature* 559:250-253.
- HACCO, I. 2021. Ramik® Green Label.

- Harper, G. A., and N. Bunbury. 2015. Invasive rats on tropical islands: Their population biology and impacts on native species. *Global Ecology and Conservation* 3:607-627.
- Hartley, L., C. O' Connor, J. Waas, and L. Matthews. 1999. Colour preferences in North Island robins (*Petroica Australis*): Implications for deterring birds from poisonous baits. *New Zealand Journal of Ecology* 23:255-259.
- Hartley, L., J. Waas, C. O'Connor, and L. Matthews. 2000. Colour preferences and coloured bait consumption by weka *Gallirallus australis*, an endemic New Zealand rail. *Biological Conservation* 93:255-263.
- Herrera-Giraldo, J. L., C. E. Figuerola-Hernández, J. F. González-Maya, N. D. Holmes, K. Swinnerton, E. N. Bermúdez-Carambot, and D. A. Gómez-Hoyos. 2019. Survival analysis of two endemic lizard species before, during and after a rat eradication attempt on Desecheo Island, Puerto Rico. *Island Conservation*.
- Herring, G., C. A. Eagles-Smith, R. Wolstenholme, A. Welch, C. West, and B. A. Rattner. 2022. Collateral damage: Anticoagulant rodenticides pose threats to California condors. *Environmental Pollution* 311: 119925:9 pp.
- Hofstadter, D. F., N. F. Kryshak, M. W. Gabriel, C. M. Wood, G. M. Wengert, B. P. Dotters, K. N. Roberts, E. D. Fountain, K. G. Kelly, J. J. Keane, S. A. Whitmore, W. J. Berigan, and M. Z. Peery. 2021. High rates of anticoagulant rodenticide exposure in California barred owls are associated with the wildland–urban interface. *Ornithological Applications* 123.
- Hopf-Dennis, C., S. Kaye, N. Hollingshead, M. Brooks, E. Bunting, and N. Abou-Madi. 2022. Prevalence of Anticoagulant Rodenticide Exposure in Red-tailed Hawks (*Buteo jamaicensis*) in New York State and Diagnostic Utility of Russell Viper Venom Test for Detecting Associated Coagulopathies (Pre-print). ResearchSquare.
- Howald, G., C. J. Donlan, K. R. Faulkner, S. Ortega, H. Gellerman, D. A. Croll, and B. R. Tershy. 2009. Eradication of black rats *Rattus rattus* from Anacapa Island. *Oryx* 44:30-40.
- Hrouzková, S., and E. Matisova. 2012. Endocrine disrupting pesticides, Chapter 5. Pages 99-126 in *Pesticides - Advances in Chemical and Botanical Pesticides*.
- IPCS. 1992. Brodifacoum, Monograph 077, Inchem. International Programme on Chemical Safety.
- \_\_\_\_\_. 2005. Health and Safety Guide No. 93 Brodifacoum. International Programme on Chemical Safety.
- Jouventin, P., J. Bried, and T. Micol. 2003. Insular bird populations can be saved from rats: a long-term experimental study of white-chinned petrels *Procellaria aequinoctialis* on Ile de la Possession (Crozet archipelago). *Polar Biology* 26:371-378.
- Kalinin, S., N. Marangoni, K. Kowal, A. Dey, K. Lis, S. Brodsky, R. van Breemen, Z. Hauck, R. Ripper, I. Rubinstein, G. Weinberg, and D. L. Feinstein. 2017. The long-lasting rodenticide brodifacoum induces neuropathology in adult male rats. *Toxicological Sciences* 159:224–237.
- Lettoof, D. C., M. T. Lohr, F. Busetti, P. W. Bateman, and R. A. Davis. 2020. Toxic time bombs: Frequent detection of anticoagulant rodenticides in urban reptiles at multiple trophic levels. *Science of the Total Environment* 724: 138218:7 pp.
- Love, R. L., N. Sharma, and K. Chong. 2019. Unusual presentation of haemoptysis following accidental inhalation of the 'superwarfarin' rodenticide brodifacoum. *BMJ Case Report* 12:e230044.
- Marples, N. M., T. J. Roper, and D. G. C. Harper. 1998. Responses of wild birds to novel prey: evidence of dietary conservatism. *Oikos* 83:61-165.
- Masuda, B. M., P. Fisher, and B. Beaven. 2015. Residue profiles of brodifacoum in coastal marine species following an island rodent eradication. *Ecotoxicology and Environmental Safety* 113:1-8.
- Masuda, B. M., P. Fisher, and I. G. Jamieson. 2014. Anticoagulant rodenticide brodifacoum detected in dead nestlings of an insectivorous passerine. *New Zealand Journal of Ecology* 38:110-115.

- Mauldin, R. E., G. W. Witmer, S. A. Shriner, R. S. Moulton, and K. E. Horak. 2020. Effects of brodifacoum and diphacinone exposure on four species of reptiles: tissue residue levels and survivorship. *Pest Management Science* 76:1958-1966.
- Miño, H. R., Ľ. I. Korytár, E. Holotová, M. Ondrašovič, T. Pošiváková, P. Korim, and L. Takáč. 2019. Potential health risk to humans related to accumulation of brodifacoum and bromadiolone in the wheat grown on rodenticide contaminated soil. *Folia Veterinaria* 63:18-26.
- Murphy, E. C., B. K. Clapperton, P. M. F. Bradfield, and H. J. Speed. 1998. Brodifacoum residues in target and non-target animals following large-scale poison operations in New Zealand podocarp-hardwood forests. *New Zealand Journal of Zoology* 25:307-314.
- Murray, M. 2017. Anticoagulant rodenticide exposure and toxicosis in four species of birds of prey in Massachusetts, USA, 2012–2016, in relation to use of rodenticides by pest management professionals. *Ecotoxicology* 26:1041–1050.
- . 2020. Continued anticoagulant rodenticide exposure of red-tailed hawks (*Buteo jamaicensis*) in the Northeastern United States with an evaluation of serum for biomonitoring. *Environmental Toxicology and Chemistry* 39: 2325–2335.
- Musto, C., J. Cerri, D. Capizzi, M. C. Fontana, S. Rubini, G. Merialdi, D. Berzi, F. Ciuti, A. Santi, A. Rossi, F. Carsi, L. Gelmini, L. Fiorentini, G. Pupillo, C. Torreggiani, A. Bianchi, A. Gazzola, P. Prati, G. Sala, M. Apollonio, M. Delogu, A. Biancardi, L. Uboldi, A. Moretti, and C. Garbarino. 2024. First evidence of widespread positivity to anticoagulant rodenticides in grey wolves (*Canis lupus*). *Science of the Total Environment* 915:169990:11 pp.
- National Research Council. 1983. Risk assessment in the Federal government: managing the process. National Academy Press, Washington, DC.
- NCBI. 2023. PubChem Compound Summary for CID 54680676, Brodifacoum. *in* National Center for Biotechnology Information.
- Newton, K. M., M. McKown, C. Wolf, H. Gellerman, T. Coonan, D. Richards, A. L. Harvey, N. Holmes, G. Howald, K. Faulkner, B. R. Tershy, and D. A. Croll. 2016. Response of Native Species 10 Years After Rat Eradication on Anacapa Island, California. *Journal of Fish and Wildlife Management* 7:72-85.
- Niedringhaus, K. D., N. M. Nemeth, S. Gibbs, J. Zimmerman, L. Shender, K. Slankard, H. Fenton, B. Charlie, M. F. Dalton, E. J. Elsmo, R. Poppenga, B. Millsap, and M. G. Ruder. 2021. Anticoagulant rodenticide exposure and toxicosis in bald eagles (*Haliaeetus leucocephalus*) and golden eagles (*Aquila chrysaetos*) in the United States. *PLoS One* 16(4): e0246134:13 pp.
- Pain, D. J., M. D. L. Brook, and A. Jackson. 2000. Effects of brodifacoum on the land crab of Ascension Island. *Journal of Wildlife Management* 64:380-387.
- Pitt, W. C., A. R. Berentsen, A. B. Shiels, S. F. Volker, J. D. Eisemann, A. S. Wegmann, and G. R. Howald. 2015. Non-target species mortality and the measurement of brodifacoum rodenticide residues after a rat (*Rattus rattus*) eradication on Palmyra Atoll, tropical Pacific. *Biological Conservation* 185:36-46.
- Regnery, M., S. Rohner, J. Bachtin, C. Mohlenkamp, O. Zinke, S. Jacob, P. Wohlsein, U. Siebert, G. Reifferscheid, and A. Friesen. 2024. First evidence of widespread anticoagulant rodenticide exposure of the Eurasian otter (*Lutra lutra*) in Germany. *Science of the Total Environment* 907: 167938:10 pp.
- Riegerix, R. C., M. Tanner, R. Gale, and D. E. Tillitt. 2020. Acute toxicity and clotting times of anticoagulant rodenticides to red-toothed (*Odonus niger*) and black (*Melichthys niger*) triggerfish, fathead minnow (*Pimephales promelas*), and largemouth bass (*Micropterus salmoides*). *Aquatic Toxicology* 221:105429.
- Samaniego-Herrera, A., J. C. Russell, D. Choquenot, A. Aguirre-Muñoz, and M. N. Clout. 2014. Invasive Rodents on Tropical Islands: Eradication Recommendations from Mexico. *Proceedings of the Vertebrate Pest Conference* 26:43-50.

- Siers, S. R., A. B. Shiels, S. F. Volker, K. Rex, and W. C. Pitt. 2020. Brodifacoum residues in fish three years after an island-wide rat eradication attempt in the tropical Pacific. *Management of Biological Invasions*. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services, *Invasivesnet* 11:105-121.
- Spurr, E. B., and K. W. Drew. 1999. Invertebrates feeding on baits used for vertebrate pest control in New Zealand. *New Zealand Journal of Ecology* 23:167-173.
- Sztukowski, L. A., and D. C. Kesler. 2012. Bait consumption by sooty terns: Implications for island eradication programmes. *Bird Conservation International*:9 pp.
- The Danish Environmental Protection Agency. 2024. Endocrine disruptor lists. The Danish Environmental Protection Agency.
- Thibault, J.-C. 1995. Effect of predation by the black rat *Rattus rattus* on the breeding success of Cory's shearwater *Calonectris diomedea* in Corsica. *Marine Ornithology* 23:1-10.
- Underwood, E. L., J. Sutton, I. K. Ellis, B. Qualls, J. Zamber, and B. N. Walker. 2014. Prolonged coagulopathy after brodifacoum exposure (abstract only). *American Journal of Health-System Pharmacy* 71:639-642.
- USDA APHIS. 2009. Diphacinone-50 Product Label, February 5, 2009.
- USEPA. 1989. Risk assessment guidance for Superfund volume I, human health evaluation manual (Part A). Interim final. EPA/540/1-89/002 December 1989 United States Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.
- \_\_\_\_\_. 1991. Data Evaluation Record: Acute toxicity test for freshwater invertebrates. USEPA Office of Pesticide Programs.
- \_\_\_\_\_. 1998. Reregistration Eligibility Decision (RED) - Rodenticide Cluster, EPA738-R-98-007. Available at: <https://archive.epa.gov/pesticides/reregistration/web/pdf/2100red.pdf>. U.S. Environmental Protection Agency, Prevention, Pesticides, and Toxic Substances.
- \_\_\_\_\_. 2004. Potential risk of nine rodenticides to birds and nontarget mammals: a comparative approach. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.
- \_\_\_\_\_. 2008. Risk Mitigation Decision for Ten Rodenticides EPA-HQ-OPP-2006-0955-0753. U.S. Environmental Protection Agency Office of Pesticide Programs.
- \_\_\_\_\_. 2011. Brodifacoum-25W Conservation, EPA Registration No. 56228-36, Supplemental Label to Control and Eradicate Black Rats on Palmyra Atoll, Expired 07/31/2014. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.
- \_\_\_\_\_. 2012. Endocrine Disruptor Screening Program Universe of Chemicals and General Validation Principles. US Environmental Protection Agency.
- \_\_\_\_\_. 2015. Brodifacoum-25D Conservation, EPA Registration No. 56228-37, Supplemental Label for Control and Eradication of Roof (Black) Rats on Desecheo Island, Puerto Rico, Expired November 23, 2020. U.S. Environmental Protection Agency, .
- \_\_\_\_\_. 2016a. Brodifacoum: Human Health Risk Scoping Document in Support of Registration Review. U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2016b. Overview of Risk Assessment in the Pesticide Program <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program> Accessed 03/14/2023.
- \_\_\_\_\_. 2016c. Problem Formulation for the Environmental Fate, Ecological Risk, Endangered Species, and Drinking Water Exposure Assessments in Support of the Registration Review for Brodifacoum. U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2019a. Brodifacoum-25D Conservation, EPA Registration Number 56228-37. U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2019b. Brodifacoum-25W Conservation, EPA Registration Number 56228-36. U.S. Environmental Protection Agency.

- \_\_\_\_\_. 2020a. Chlorophacinone, Diphacinone and its Sodium Salt, Brodifacoum, Bromadiolone, Difenacoum, Difethialone; Draft Human Health Risk Assessment for Registration Review of Anticoagulant Rodenticides (EPA-HQ-OPP-2015-0768-0043). U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2020b. Seven anticoagulant rodenticides: draft ecological risk assessment for registration review. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.
- \_\_\_\_\_. 2021. Supplemental Labeling, Brodifacoum-25D Conservation, EPA Registration Number 56228-37, For control and eradication of house mice (*Mus musculus*) on Midway Atoll National Wildlife Refuge's Sand Island. U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2022a. Rodenticides Revised Tier I Update Review of Human Incidents. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.
- \_\_\_\_\_. 2022b. Supplemental Labeling, Brodifacoum-25W Conservation, EPA Registration Number 56228-36, for control and eradication of Polynesian rats on Wake Atoll. U.S. Environmental Protection Agency.
- \_\_\_\_\_. 2023a. Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity. *in*.
- \_\_\_\_\_. 2023b. Endocrine Disruptor Screening Program (EDSP) Overview U.S. Environmental Protection Agency <https://www.epa.gov/pesticides/epa-rebuilds-endocrine-disruptor-screening-program-soliciting-public-comment-new> Accessed 03/14/2023.
- \_\_\_\_\_. 2023c. Inert ingredients overview and guidance US Environmental Protection Agency <https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance> Accessed 07/28/2023.
- \_\_\_\_\_. 2024a. Ecotox Knowledgebase: Queried Brodifacoum. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.
- \_\_\_\_\_. 2024b. Endocrine Disruptor Screen Program Overview. *in* U.S. Environmental Protection Agency.
- USFWS. 2011. Palmyra Atoll National Wildlife Refuge Rat Eradication Project Final Environmental Impact Statement. U.S. Department of the Interior, U.S. Fish and Wildlife Service.
- \_\_\_\_\_. 2019. Midway Seabird Protection Project Final Environmental Assessment. United States Department of the Interior, U.S. Fish and Wildlife Service.
- \_\_\_\_\_. 2024. Midway Atoll's Seabird Protection Project. U.S. Department of the Interior, U.S. Fish and Wildlife Service.
- van Dam, J., A. P. Negri, S. Uthicke, and J. Mueller. 2011. Chemical pollution on coral reefs: Exposure and ecological effects. Pages 187-211 *in* Ecological Impacts of Toxic Chemicals (Open Access).
- Walther, B., A. Geduhna, D. Schenke, and J. Jacob. 2021. Exposure of passerine birds to brodifacoum during management of Norway rats on farms. *Science of the Total Environment* 762: 144160:8 pp.
- Wegmann, A., G. Howald, S. Kropidlowski, N. Holmes, and A. B. Shiels. 2019. No detection of brodifacoum residues in the marine and terrestrial food web three years after rat eradication at Palmyra Atoll, Central Pacific. USDA, APHIS, WS, National Wildlife Research Center - Staff Publications.
- Weir, S., S. Yu, A. Knox, L. Talent, J. Monks, and C. Salice. 2016. Acute toxicity and risk to lizards of rodenticides and herbicides commonly used in New Zealand. *New Zealand Journal of Ecology* 40:342-350.
- Weser, C., and J. G. Ross. 2013. The effect of colour on bait consumption of kea (*Nestor notabilis*): implications for deterring birds from toxic baits. *New Zealand Journal of Zoology* 40:137-144.
- WHO. 1995. Brodifacoum Health and Safety Guide. World Health Organization for the International Programme on Chemical Safety.
- Wiens, J. D., K. E. Dilione, C. A. Eagles-Smith, G. Herring, D. B. Lesmeister, M. W. Gabriel, G. M. Wengert, and D. C. Simon. 2019. Anticoagulant rodenticides in *Strix* owls indicate widespread exposure in west coast forests. *Biological Conservation* 238: 108238:8 pp.

- Witmer, G. W., J. Eisemann, and G. Howald. 2007. The use of rodenticides for conservation efforts. Pages 160-167 in D. L. Nolte, W. M. Arjo, and D. H. Stalman, editors. Proceedings of the Wildlife Damage Management Conference.
- Wolf, C. A., H. S. Young, K. M. Zilliacus, A. S. Wegmann, M. McKown, N. D. Holmes, B. R. Tershy, R. Dirzo, S. Kropidowski, and D. A. Croll. 2018. Invasive rat eradication strongly impacts plant recruitment on a tropical atoll. PLoS One 13:1-17.
- Wu, Y., X. Ye, L. Jiang, A. Wang, J. Wang, W. Yao, Y. Qin, and B. Wang. 2023. Developmental toxicity induced by brodifacoum in zebrafish (*Danio rerio*) early life stages. Birth Defects Research 115:318–326.