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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

December 29, 2011

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held November 29 - December 1, 2011 on Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products

TO: Steven Bradbury, Ph.D., Director
Office of Pesticide Programs

FROM: Joseph E. Bailey, Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Joseph E Bailey

THRU: Laura Bailey, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Laura Bailey 12/29/11

Frank Sanders, Director
Office of Science Coordination and Policy

Steven M. Knott for

Attached, please find the meeting minutes of the FIFRA Scientific Advisory Panel open meeting held in Arlington, VA on November 29 - December 1, 2011. This report addresses a set of scientific issues associated with the Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products.

Enclosure

cc:

Jim Jones
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OPP Docket

FIFRA Scientific Advisory Panel Members

Kenneth Portier, Ph.D.
Janice Chambers, Ph.D., DABT, Fellow ATS
Stephen Klaine, Ph.D.
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Greene Shepherd, PharmD

SAP Minutes No. 2011-06

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products

November 29 - December 1, 2011
FIFRA Scientific Advisory Panel Meeting
Held at the
Environmental Protection Agency Conference Center
Arlington, VA

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). The meeting minutes represent the views and recommendations of the FIFRA SAP, not the United States Environmental Protection Agency (Agency). The content of the meeting minutes does not represent information approved or disseminated by the Agency. The meeting minutes have not been reviewed for approval by the Agency and, hence, the contents of these meeting minutes do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal Government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency, Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. FQPA Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Joseph E. Bailey, SAP Designated Federal Official, via e-mail at bailey.joseph@epa.gov.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by EPA, as well as information presented by public commenters.

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Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products

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FIFRA Scientific Advisory Panel Meeting
Held at the
Environmental Protection Agency Conference Center
Arlington, VA

Kenneth M. Portier, Ph.D.
FIFRA SAP Chair
FIFRA Scientific Advisory Panel
Date: DEC 2 9 2011

Joseph E. Bailey
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: DEC 2 9 2011

Federal Insecticide Fungicide and Rodenticide Act
Scientific Advisory Panel Meeting
November 29 - December 1, 2011

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INTRODUCTION

The Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) has completed its review of the Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products. Advance notice of the meeting was published in the *Federal Register* on September 7, 2011. The review was conducted in an open panel meeting held in Arlington, VA, on November 29 - December 1, 2011. Dr. Kenneth Portier chaired the meeting. Joseph E. Bailey served as the Designated Federal Official.

The EPA's 2008 Risk Mitigation Decision for Ten Rodenticides (RMD) concluded more than a decade of Agency review of commensal rodenticides. The RMD concluded that registrants of commensal rodenticide products needed to adopt certain risk mitigation measures in order to meet the FIFRA registration standard of not causing unreasonable adverse effects on the environment.

In 2008, EPA gave registrants of commensal rodenticide bait products three years to research, develop, and register new consumer/homeowner products that adopted these risk mitigation measures designed to greatly reduce child, pet, and non-target wildlife exposure to rodenticides. The Agency drafted a proposed Notice of Intent to Cancel (NOIC) for 20 consumer/homeowner rodenticide products for which registrants have refused to voluntarily adopt the risk mitigation measures. The Agency sought advice and recommendations from the SAP on the following scientific issues associated with the proposed NOIC:

- EPA's evaluation of human and pet incidents of accidental exposure to rodenticides.
- EPA's evaluation of ecological incidents of accidental exposure to rodenticides.
- The differences in uptake and clearance of first-generation anticoagulant rodenticides, non-anticoagulant rodenticides, and second-generation anticoagulant rodenticides, in target and non-target wildlife.
- EPA's ecological risk assessments for rodenticides: ecological risks of first-generation anticoagulant rodenticides, non-anticoagulant rodenticides, and second-generation anticoagulant rodenticides.
- The differences in secondary ecological exposure between first-generation anticoagulant rodenticides, non-anticoagulant rodenticides, and second-generation anticoagulant rodenticides.

PUBLIC COMMENTS

Oral Statements were presented as follows:

On behalf of Reckitt Benckiser LLC:

Bill Mordan, Senior Vice President and General Counsel, Reckitt Benckiser Group plc
Richard Kingston, Pharm D, SafetyCall
James McCluskey, Ph.D., M.D., M.P.H., University of South Florida
Ahna G. Brutlag, D.V.M., M.S., SafetyCall
Anne Fairbrother, D.V.M., Ph.D., Exponent, Inc.
Richard Stroud, D.V.M., M.S., Stroud Consulting
Alan P. Buckle, Ph.D., University of Reading, School of Biological Sciences
Hans-Joachim Pelz, Ph.D., Julius Kuhn Institut
Colin V. Prescott, Ph.D., Director, Vertebrate Pests Unit, University of Reading
Richard Wade, Ph.D., M.P.H., University of California, Exponent, Inc.

Gale Lively, Executive Vice President on behalf of Louisville Apartment Association
John Lublinkhof, Ph.D., on behalf of Bell Laboratories, Inc.

Written Statements were provided by:

Anonymous
Joseph Manuppello, People for the Ethical Treatment of Animals
Steve Torres, State of California
Lawrence E. Culleen, Arnold and Porter
Julio Fuentes, Florida State Hispanic Chamber of Commerce
Thomas Schmit, Liphatech, Inc.
John Lublinkhof, Bell Laboratories, Inc.
John M. Skillen, Responsible Industry for a Sound Environment
Omar Duque, Illinois Hispanic Chamber of Commerce
Barry Paceley, Arcadia Neighbor to Neighbor
Gale Lively, Louisville Apartment Association
Michael Swoyer, Kansas City Health Department
Patrick Shuttleworth, Camden County (NJ) Department of Health & Human Services
L'Tanya Williamson, Newark Department of Child and Family Well-Being
Thomas Matte, New York City Department of Health and Mental Hygiene
Hal Ambuter, Reckitt Benckiser
Frank Pacheco, Housing Authority of the City of Pueblo
Andrea Ortiz, The Maverick Academy
Todd Butzow, Bell Laboratories, Inc.
Beth L. Law, Consumers Specialty Chemicals Association
Iraida Afanador, City of Camden (NJ), Department of Code Enforcement (post-public comment period)
Lawrence E. Culleen, Arnold and Porter (post-public comment period)

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

Charge Question 1: *Does the Agency's analysis of the mammalian toxicity studies and human incident reports provide a reasonable basis for concluding that exposure to warfarin, brodifacoum, difethialone and/or bromethalin can cause health effects in individuals who ingest these rodenticides? Are the adverse effects described in the children's incident reports [e.g., anemia, melena (bloody stool), hematemesis (vomiting of blood)], credible consequences of exposure to these active ingredients? Please provide the basis for your conclusions.*

The Panel believed that the mammalian toxicity studies do provide a reasonable basis for concluding that exposure to warfarin, brodifacoum, difethialone and bromethalin can cause health effects in people who might ingest these rodenticides. The commonalities in the physiology among mammals, including the laboratory rodents and humans, indicate that there are common targets for these toxicants. It is possible for adverse health effects to result if a sufficiently large ingestion occurs. There is no question about the ability of anticoagulant rodenticides (including warfarin, brodifacoum and difethialone) to inhibit the action of vitamin K epoxide reductase which results in a decrease in the body's ability to clot blood. However, available evidence suggests that the vast majority of exposures to first and second generation anticoagulant rodenticide products by young children will not result in a clinically significant coagulopathy or bleeding. If the toxic threshold is exceeded, there is a widely available laboratory test and an antidote (vitamin K_1) with which clinicians are familiar because of the therapeutic use of warfarin.

Bromethalin is not an anticoagulant and would not be expected to produce bleeding complications. Instead, it is a metabolic poison that disrupts oxidative phosphorylation in the mitochondria, which leads to increased sodium inside neurons. Clinically, this results in swelling of the brain (cerebral edema) and could ultimately lead to death. In general, severe bromethalin poisonings are very concerning for clinicians because of less human experience with them and, unlike the anticoagulant rodenticides, there is no specific diagnostic test or antidote. Given that bromethalin targets the central nervous system (CNS), there is concern that the developing brain of young children may be particularly susceptible to the effects of bromethalin.

Charge Question 2: *The human incident report summarizes a number of data and information sources used in the analyses and reviews conducted. Based on the incident report analysis, EPA has concluded that there are a large number of rodenticide exposure incidents that involve children less than 6 years old. While exposure generally results in no clinical harm to children, the exposures to rodenticides have the potential to result in severe outcomes and/or require medical care or follow-up. Does the SAP concur with the EPA's conclusions regarding the extent of exposures, potential severity of effects, and degree of risks posed to humans? Are the conclusions reached reasonably supported by the data analysis? Please explain the basis of your position.*

Incident reports provide important information because they reflect potential exposures and adverse consequences in humans who are accidentally exposed to toxicants, including the subject rodenticides, and therefore, the incident reports should not be ignored. However, the incident reports should be viewed with a great deal of caution since the incident data come from

several sources, all of which have strengths and limitations. For most incident reports, an accurate measure of true ingestions is lacking and exposures may be over-reported or under-reported. Exposure to rodenticides have the potential to result in severe outcomes; however, there appears to be relatively little data included in the incident reports that verify that exposures to people, including children, have occurred that have been of a magnitude to be considered major incidents. EPA has not established a quantitative level of risk for severe outcomes and, hence, it is difficult to concur with EPA's "degree of risks" posed to humans. Based on the available data, the Panel agreed with the EPA's assertion that exposure generally results in no clinical harm to children. While the possibility of harm exists, it rarely occurs except in the setting of intentional ingestions or malicious poisoning. This relatively low risk to humans needs to be carefully weighed against the risks associated with poor rodent control. One Panel member stated that it is important to reduce the opportunity for children to be exposed to rodenticides and that it is consistent with the EPA's efforts to protect children's health and also consistent with recommendations of the EPA's Children's Health Protection Advisory Committee that the Agency take actions to reduce children's exposures to chemicals with toxicity concerns.

Charge Question 3: *Based on the human incident report, EPA concludes that the use of conforming rodenticide products will reduce the risk rodenticides pose to humans by reducing the opportunity for exposure. Is it reasonable to expect that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of humans to commensal rodenticide products? Please provide the basis for your conclusions.*

The Panel stated that it is reasonable to expect that limiting consumer use to conforming rodenticide products, if used according to the product labeling, will generally reduce the opportunity for exposure of humans to these particular rodenticides because of the restricted ability to contact the baits. If the bait stations are not used correctly, then exposure to the rodenticides is still likely and adverse effects may occur. EPA is urged to give further consideration to the likelihood that consumers will not use the bait stations for all the rodenticides placed in their homes. There is concern that the potential additional expense of providing enough bait stations or the inconvenience of loading the bait stations might preclude consumer adherence to label directions regarding proper rodenticide application. Poor health outcomes associated with unintentional rodenticide exposures in children are rarely observed and any reduction of outcome rates would, therefore, be modest. Some data presented suggest that human incident reports have decreased for post-mitigation compliant rodenticide products, compared to pre-mitigation compliant products for comparable time periods. While encouraging, this trend has not been analyzed for significance.

The Panel urged EPA to make certain that rodent control can be adequately maintained for protection of human health following the proposed cancellations. The Panel urged EPA to make certain that a thorough and well-researched assessment of the public health issues associated with a potential reduction in rodent control (e.g., the potential for increases in rodent-borne diseases, bites) is provided by the Department of Health and Human Services (DHHS), and that this assessment be used in the overall risk assessment of the rodenticide products under consideration in this NOIC.

Charge Question 4: *The pet incident report summarizes a number of data and information sources used in the analyses and reviews conducted. The EPA concludes that there is a high frequency of reported pet incidents involving rodenticides, many of which result in severe outcomes; this conclusion is further supported by the information reported in the open literature as well as the characterization of primary acute risk. Does the SAP concur with EPA's conclusions of the risks posed to pets by non-conforming rodenticide products? Are the conclusions reached reasonably supported by the data analysis? Please explain the basis of your position.*

The Panel concurred that the results from the database searches and literature provided by EPA and others support the conclusion that exposure to, and adverse effects from, rodenticides, including anticoagulant rodenticides, have occurred in pets in the United States from 1999 to 2010. However, the Panel's response provides only the risk perspective, and does not include the benefit perspective of the analysis. The database results and literature review were interpreted as observational data, not an assessment of risk, *per se*; consequently, they do not support use of the terms "risk" or "high frequency" in the NOIC, at least to the extent that those terms imply that a risk assessment was conducted. Recent evidence for numerous incidents involving pets and non-conforming rodenticides appears to be adequate and brodifacoum use in and around the home has been involved in the majority of reports. Decreasing over-the-counter availability of brodifacoum is likely to reduce adverse pet events associated with it, if properly applied. The potential consequences of increased use of the non-anticoagulant rodenticide bromethalin are unknown and worrisome due to the lack of diagnostic tests and effective treatment options for bromethalin intoxication. The Panel noted additional risk concerns not mentioned in the NOIC, such as the increased risks associated with a choking hazard from bait blocks, exposure to a 1 ounce bait block and gastrointestinal trauma from bait station ingestion, particularly for dogs.

Charge Question 5: *The pet analysis has relied on the assessment of risks to wildlife from primary exposure as one line of evidence to characterize primary acute risk to pets from non-conforming rodenticide products. Is it reasonable to conclude that risks to pets are similar to risks to non-target mammalian wildlife, assuming comparable exposures? Please explain the basis of your conclusions.*

The Panel agreed that, to the extent that the mechanisms of action (inhibition of "recycling" of vitamin K_1, uncoupling oxidative phosphorylation, and increased circulating 25-hydroxy cholecalciferol causing hypercalcemia) are the same in pet and other non-target mammals, it is reasonable to conclude that hazards to pets and other non-target mammals are similar, but not the same. The literature supports the notion that the "toxic dose" on a mg/kg body weight basis varies among mammals, so the term comparable must account for this dose difference to arrive at comparable risk. For the rodenticides under review, published experimental studies provide information on dose levels that produce adverse outcomes in dogs, cats, and, in some instances, other pets. Use of this pet-specific data may be more appropriate than extrapolation of risk from non-target mammalian wildlife and would better address potential differences in sensitivity among species and between different rodenticides. The Panel stated that it is generally reasonable to conclude that risks to pets are similar to risks to non-target mammalian wildlife of comparable body sizes; however, the mammalian body weight groups of 15, 35, and 1,000 grams used to assess primary exposure risk are not practical for pets except in

the case of the very smallest pets. The 1,000 and 3,000-gram size mammalian classes included in the secondary exposure risk assessment provide a better approximation of small dogs and cats, but not for larger pets.

Charge Question 6: *Based on the pet incident report, EPA concludes that the use of conforming rodenticide products will reduce the opportunity for exposure of pets to rodenticides. Is it reasonable to expect that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of pets to commensal rodenticide products? Please provide the basis for your conclusions.*

The Panel did not agree with EPA that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of pets to commensal rodenticide products. They concluded that the pet incident reports demonstrate that residential consumers in general do not read and/or follow label directions for current rodenticides and hence, would not be any more likely to do this for rodenticide products formulated in block form. To the extent that conforming rodenticide products are provided outside of bait stations, the pet incident report does not support the conclusion that the opportunity for exposure of pets to commensal rodenticide products is likely to be reduced. To the extent that conforming rodenticides are provided solely in tamper-proof bait stations that actually reduce exposure to dogs and other pets, the above conclusion may change. Use of rodenticides in bait stations will decrease the ease of accessibility and likely decrease the number of exposures involving pets, but use of them will not completely eliminate exposures, especially with dogs.

Charge Question 7: *The EPA has conducted a deterministic risk assessment to evaluate the risks of acute toxicity to non-target mammals and birds from primary exposure to non-conforming rodenticide products. In its assessment, EPA calculated risk quotients on an acute oral dose and acute dietary exposure basis for birds and mammals and further characterized the opportunity for exposure at lethal levels based on factors including the number of days required to feed and the mass of pesticide required to be consumed to reach lethal thresholds. Using the best available data, EPA made assumptions relative to toxicity, accumulation, and clearance of the pesticides that are material to the exposure and effects modeling in the deterministic primary risk assessment.*

a. Please comment on the reasonableness of the following aspects of EPA's primary exposure deterministic risk assessment:

Selection of toxicity endpoints for species common to all assessed chemicals in light of the incomplete overlap across available data sets - Death is used as an endpoint as it is definitive, and regulatory requirements have resulted in the generation of such data for the test compounds in question. Regrettably, data for other adverse outcomes (e.g., overt signs of toxicity, frank bleeding, bruising, hematomas, coagulopathy, histopathological lesions, and other sublethal measures related to the mechanism of action or impending death) are not available for all of the compounds in question, and their significance is more challenging to interpret. In contrast to the Agency's selection of uniform species, a better approach would be to conduct chemical-specific assessments with conceptual models that identify receptors of interest for a refined risk assessment. The receptors should include target commensal rodents and non-target birds and

mammals. If time constraints dictated a more limited screening assessment, the Agency should consider requiring the registrant to provide a refined assessment for each compound with a clear conceptual model identifying specific receptors of interest and uncertainty factors where data gaps occur. A species sensitivity distribution provides a more quantitative approach which, in turn, would provide a quantitative estimate of uncertainty.

The current approach is likely to underestimate risk to more sensitive species, but since the level of concern (LOC) for the second generation anticoagulant rodenticides (SGARs) brodifacoum and difethialone is exceeded in less sensitive test species (e.g., quail, mallards), the decision to restrict SGARs based on these data will likely protect more sensitive wildlife species. A problem in the analysis of the first generation anticoagulant rodenticides (FGARs) (i.e., chlorophacinone, diphacinone) is the exposure scheme used in the avian and mammalian acute oral toxicity tests where a single oral dose or multiple doses are administered in a 24-hour period. As noted by EPA, the toxicity of FGARs increases by nearly two orders of magnitude when the dose is administered for 5 days. Therefore, acute oral toxicity tests for FGARs may greatly underestimate toxicity.

The use of allometric toxicity scaling approaches for birds - The use of allometric toxicity scaling in birds is generally reasonable and warranted. It is well-accepted in the field of avian medicine for the calculation of drug dosages given the lack of pharmacokinetic data for therapeutics for most avian species. In lieu of direct data for each species of concern, allometric scaling is the best available approach to address metabolic differences among birds of different sizes and taxonomic groups, but caution should be used in estimating LD_{50} values for very large or very small bird species or for taxonomic groups poorly represented in the base dataset. While allometric scaling is necessary for this deterministic assessment due to data gaps, the Agency should pursue physiologically-based pharmacokinetic (PBPK) models that estimate dose within predators following oral exposure.

The reliance on mammalian first order liver or plasma elimination half lives to estimate whole body wildlife (birds and mammals) elimination rates for anticoagulants and bromethalin, respectively - For the anticoagulant rodenticides, the use of first order liver elimination half-life is a reasonable approach for the initial estimation of whole body elimination rates, given the issues and limitations discussed in the EPA White Paper, "Risks of Non-compliant Rodenticides to Non-target Wildlife." However, it was not clear why a probabilistic approach was not used to quantify liver concentrations of individual compounds. Only one study in rats was used in the accumulation calculations and the rationale for this limitation was not clear. Sufficient data were available for a probabilistic measurement for brodifacoum. For the other compounds, specific safety factors could be used when data were not present and this approach would have provided a more quantitative assessment. In addition, first order assumptions likely underestimate clearance, since a two compartment model appears to be more realistic. The Panel recommended that the Agency pursue development and use of PBPK models to estimate levels in the liver of primary and secondary consumers following oral exposure. Although first order kinetic assumptions likely underestimate clearance, the assumption of whole animal consumption by predators probably provides some conservatism for the uncertainty of this assumption.

The use of the time required and the consumption of rodenticide mass required to reach lethal thresholds as a means of comparing the relative risks of acute mortality following consumption of rodenticide bait - EPA's approach assumes that non-target species consume only bait. This is a worst case exposure scenario, and highly conservative. Primary bait ingestion of high potency rodenticides (i.e., requiring consumption of less mass) yield large risk quotients (RQs) (body burden:LD_{50} ratios), and pose the greatest risk to non-target birds. The calculated RQs for SGARs and bromethalin for birds are large, and these baits might evoke toxicity and lethality with a single day exposure. Even warfarin bait poses a significant hazard to a small passerine exposed for just 1 day. With exposure durations of greater than 1 day, the likelihood of SGARs, bromethalin and even FGARs evoking lethality increases. As non-target primary consumers are less likely to feed exclusively on rodenticide bait in lieu of natural food items, compounds that do not provide a lethal dose in a single feeding should pose less risk. For non-target mammals, all of the formulations are hazardous and could possibly evoke lethality if consumed exclusively for as little as 1 day. The relative contribution to dietary exposure from consumption of invertebrates that bioaccumulate rodenticides is uncertain.

Charge Question 7b - *In addition, does the Panel concur with EPA's analysis and conclusion that use of non-conforming rodenticide products (i.e., not in bait stations) can cause adverse effects to non-target wildlife? Please provide a basis for your conclusions.*

The Panel did concur with EPA's analysis and conclusion that use of non-conforming rodenticide products can cause adverse effects to non-target wildlife. Direct consumption of rodenticide bait appears to be responsible for death of non-target wildlife species in rural and urban/suburban settings that may be related to homeowner use. Bait in the form of pellets or forms otherwise not contained within a bait station undoubtedly enhance the likelihood of ingestion by non-target primary consumers. In turn, the more primary consumers that contain residues, the more widespread contamination of the food chain will be through secondary and possibly tertiary exposures in predators and scavengers.

Charge Question 7c - *Is it reasonable to expect that placing rodenticide products in tamper resistant bait stations with formulations expected to remain in the bait station will generally reduce the opportunity for primary exposure of wildlife to commensal rodent control products? Please provide a basis for your conclusions.*

The Panel believed it is reasonable to expect that rodenticide placed inside tamper resistant bait stations will reduce the likelihood of wildlife (e.g., grey squirrels, chipmunks, passerine birds) accessing the bait. The opportunity for primary exposure will continue to exist for small non-targeted mammals and birds and consideration should be given to the impact of invertebrate access, bioaccumulation and subsequent consumption by mammals and birds.

Charge Question 8a *- The EPA has conducted a deterministic risk assessment to evaluate risks of acute toxicity to non-target mammals and birds from secondary exposure to non-conforming rodenticide products. In its exposure estimate, EPA used both calculated theoretical contamination levels in prey and available empirical data. EPA also characterized the secondary exposure risk using secondary feeding studies and factors including the number of contaminated animals required to be consumed to reach lethal exposure thresholds. For these analyses, using the best available data, EPA made assumptions relative to toxicity, accumulation, and clearance of the pesticide that are material to the exposure and effects modeling in the deterministic secondary exposure risk assessment.*

a. Please comment on the reasonableness of the following aspects of EPA's secondary exposure deterministic risk assessment.

The use of a theoretical body burden calculation together with empirical whole body residue data to produce a reasonable range of estimated exposures for secondary exposure pathways - Based on existing data and given that there are many uncertainties in determining body burden in prey species, the methods/approach used in the EPA's risk assessment are generally appropriate for this problem. The overall weight of available evidence supports the Agency's conclusions, even considering the well-addressed uncertainties.

The use of the number of prey items required to reach lethal thresholds as a means of comparing the relative risks across the assessed rodenticides of acute mortality following consumption of contaminated prey - The Panel believed that assessing risk in terms of number of contaminated prey items ingested by wildlife species is a reasonable approach. However, a level of uncertainty does exist for both first and second generation anticogulants in this assessment due to differences in sensitivity between the standard test species (quail and mallard) and birds of prey. There is also uncertainty associated with the risk of secondary toxicity to bromethalin since tissue retention is unknown.

The conclusion that the results of predator / scavenger feeding studies are consistent with the findings of the deterministic secondary risk assessment - It is clear from these studies that brodifacoum, in particular, poses a significant secondary hazard. However, while the overall secondary risk assessment determined a lower risk to avian predators/scavengers from diphacinone and chlorophacinone, this lower risk from consumption of FGARs by birds of prey is not well supported by the cited feeding studies and does not match the deterministic predictions provided by EPA. The Panel suggested EPA reassess the significance of these studies. Feeding studies, in general, are more likely to underestimate than overestimate effects of all anticoagulant rodenticides in wild birds and mammals for two reasons:
1) predators/scavengers in the wild may be exposed to contaminated prey for longer time periods than in controlled feeding studies and 2) animals in the wild are subjected to far more physical stress than animals maintained in a laboratory.

The use of a standardized set of avian toxicity endpoints (i.e., species tested across all the assessed chemicals) in light of information on diphacinone suggesting that raptors may be more sensitive than the surrogate avian species used in the risk assessment - Regarding the conclusions that SGARs present a high risk to secondary consumers such as raptors, the Panel believed the decision to restrict the use of SGARs is warranted given that the standard test species used are indeed likely to be less sensitive than raptors and that the LOC was exceeded for the test species. Reliance on standardized avian toxicity endpoints using less sensitive species is likely to underestimate the risk to birds of prey from both FGARs and SGARs making it difficult to determine if FGARs present less risk than SGARs to birds of prey.

Charge Question 8b *- Does the Panel concur with EPA's analysis and conclusion that consumption of living or dead rodents poisoned by brodifacoum or difethialone presents a greater opportunity for adverse effects to non-target wildlife compared with the rodenticides warfarin, diphacinone, chlorophacinone, or bromethalin? Please provide a basis for your conclusions. Does the Panel concur that cancellation of products containing brodifacoum and difethialone sold to residential consumers will reduce the opportunity for secondary exposure for wildlife to rodenticides? Please provide a basis for your conclusions.*

The case for a high risk to non-target wildlife from brodifacoum exposure is well supported. The conclusions that FGARs present a lesser risk to non-target wildlife, particularly birds of prey, may be flawed due to the reliance on test species that may have lower sensitivities to FGARs than birds of prey. The conclusion that bromethalin presents a lesser risk to non-target wildlife may be flawed due to limited information on tissue persistence of bromethalin. Bromethalin intoxications are very difficult to diagnose, detect, and treat, and there is not enough evidence to support its suggested use as a lower-risk alternative to SGARs. The cancellation of products containing SGARs would probably reduce the overall opportunity for secondary exposures involving wildlife; however, more research is needed to determine the risks of difethialone and potentially increased exposures of non-target wildlife to FGARs and bromethalin. In general, the analysis presented by the EPA did not include real numerical quantifications of risk, and there seems to be a great degree of uncertainty for some components of the risk assessment. While these uncertainties can be better addressed in the case of brodifacoum, where more data are available, the application of some uncertainty/safety factors would be needed for the other compounds under consideration. In addition, it is not clear that brodifacoum and difethialone should be considered together since their overall risks are not similar.

The incident data and exposure data provide strong evidence that SGAR use, particularly brodifacoum, in urban and suburban areas has the potential to impact non-target wildlife, and that brodifacoum contamination of the terrestrial food chain is widespread. Cancellation of products containing brodifacoum for residential use should decrease the contamination of the food chain with this rodenticide which poses a high risk of mortality to secondary consumers. The path of SGARs through the food chain is unknown. Whether professional use of SGARs will continue to facilitate entry of these chemicals into the food chain cannot be determined at this time; hence, evaluation of the risk of SGARs to non-target secondary consumers should be continued. Unknown is the extent to which risk to secondary consumers and birds of prey, in

particular, may increase as residential use of chlorophacinone, diphacinone and bromethalin increases.

Charge Question 9a *- Incident data demonstrate that rodenticide use can result in wildlife mortality, and that such wildlife mortalities occur in urban and suburban areas. Based on this incident data, EPA has concluded that consumer use of rodenticides in urban and suburban areas may be a significant contributor to the wildlife mortalities attributable to rodenticides. The EPA also determined that both primary and secondary poisonings have been documented.*

As part of its analysis of incidents, EPA analyzed the available incident data in order to associate incidents with specific land use categories, i.e., agricultural, urban, suburban areas. In performing this analysis, EPA relied on the information in incident reports identifying associated habitat or on the address reported for the incident and then used remote sensing information to assign a land use category with the incident. Please comment on the reasonableness of this approach to using location information to support the conclusion that use of the commensal rodenticides addressed in the draft NOIC causes wildlife mortalities in urban and suburban areas, as well as rural areas.

It seems reasonable to assume that use of these domestic products to control commensal rodents would be highest in areas with dense populations of people. However, rodenticides are also deployed by professionals representing commercial and institutional entities in urban and suburban areas and it is not clear how one would separate domestic from commercial/institutional usage as sources in urban and suburban land use areas. At issue is the extent to which wildlife coexisting in urban and suburban land use areas experiences increased exposure to and poisoning by the products listed in the NOIC. EPA addressed this issue by sorting the incidents of rodenticide-linked wildlife poisonings (primarily data from the Ecological Incident Information System (EIIS)) into land use categories, based on the density of human development. The majority of reported incidents were linked to brodifacoum and the evidence was quite compelling. The evidence for a small number of incidents for the other SGAR compound, difethialone, are consistent with those of brodifacoum and primary and secondary classified incidents were all in urban/suburban environments. A small number of incidents were also reported for warfarin, bromethalin, chlorophacinone and diphacinone, but no clear spatial trends were evident for those compounds.

The Panel discussed the various sources of uncertainty in the incident reporting system data. These uncertainties suggest that it is possible that some diagnoses of anticoagulant poisoning in wildlife are incorrect or missed. However, there is no reason to believe that the incidence of incorrect diagnoses should be related to the habitat category and, therefore, significantly bias the results of the spatial analysis. The analysis of the published literature agrees with the analysis of the EIIS data which includes some incidents also reported in the published literature of the U.S. and other countries, and establishes that brodifacoum is overwhelmingly the compound associated with both primary and secondary non-target wildlife mortality. There are consistent trends of more reported SGAR-related mortalities in urbanized environments. These data lend support to the idea that there is, indeed, a complete exposure pathway for secondary poisoning of avian predators from application of rodenticides, at least for owls, and that the prey species of primary exposure is the targeted Norway rat. This exposure

pathway likely accounts for a proportion of the wildlife incidents and for reports of hepatic SGAR residues reported in dead secondary consumers found in urban/suburban land use areas. Of relevance to the above point, both avian and mammalian predators appear to be increasingly adapting to urban and suburban environments.

Charge Question 9b *- EPA analyzed the available incident data in order to differentiate primary and secondary wildlife mortality. For this analysis, EPA relied on information on the dietary requirements of the moribund species and any identified gut contents when available. Does the Panel find this approach a reasonable way to evaluate the occurrence of primary and secondary toxicity as causes of wildlife mortality? Please provide the basis for your conclusions.*

Separating wildlife mortality incidents caused by rodenticide exposure into primary and secondary events based on knowledge of dietary preferences is a reasonable approach. The Panel urged caution be used when relying on the presence of any identified gut contents in omnivorous species. Incidents involving birds of prey can be almost exclusively categorized as secondary poisoning as it is highly improbable that any of the raptor species would feed on bait pellets or blocks. Mammalian predators and scavengers are most likely to be exposed secondarily through predation or scavenging, but could conceivably be attracted to and exposed through consumption of certain pellet or bait block formulations (e.g., those with fish scents/flavors) so categorizing them is more problematic. Omnivores could conceivably be exposed through consumption of contaminated insects, treated grains, pellets or bait blocks as well as through predation or scavenging of poisoned or intoxicated target commensal rodents and, thus, categorizing them is also problematic. Species which are primarily herbivorous such as songbirds, squirrels and non-commensal rodents would be exposed to rodenticides almost exclusively through consumption of treated grain, pellets or bait blocks. For omnivorous and/or scavenging species, analysis of the dead animal's stomach contents will not necessarily determine primary or secondary exposure due to the delayed onset of signs caused by anticoagulant rodenticides. In summary, this approach of separating primary and secondary poisonings by diet is basically sound, but post-mortem evidence from gut contents must be interpreted cautiously.

Charge Question 10 *- EPA requires registrants of commensal rodent control products to demonstrate that their products meet criteria for efficacy. The registrants of conforming rodenticide products have submitted such data to EPA, and EPA has determined that their products meet these criteria. Do the meeting of these efficacy performance criteria and EPA's analysis of the effectiveness of conforming rodenticide products reasonably support conclusions that conforming rodenticide products provide effective options for chemical control of commensal rodents by nonprofessional users? If you conclude that conforming rodenticide products do not provide effective options for chemical control of commensal rodents by nonprofessional users, please discuss to what extent the following requirements affect the availability to consumers of effective options for control of commensal rodents:*

- *The requirement that rodenticides sold to residential consumers must include tamper-resistant bait stations;*
- *The requirement that rodenticides sold to residential consumers must be in forms (e.g. bait blocks) which are reasonably expected to remain within the bait station; and*

- *The requirement that rodenticides sold to residential consumers not contain the active ingredients brodifacoum, difethialone, bromadiolone, or difenacoum.*

Please provide the basis for your conclusions.

The Panel did not believe that efficacy data alone can be used to conclude that conforming rodenticide products are an effective option for the control of commensal rodents by nonprofessional users. Prior rodenticide exposure and rodenticide resistance (via either genetic and/or behavioral changes) may account for some, but not all, of the variation in control effectiveness. Environmental realities, including, but not limited to, access to areas where rodents are normally found, structural condition of the home or building, availability of alternate food sources, learned foraging behaviors, variation in wild strains and neophobia, all play a part in the effectiveness of a rodent control effort. It is not unreasonable to expect that certain rodenticide and rodenticide formulations will perform better in certain environments and be less effective in other environments.

Tamper resistant bait stations provide some increased level of safety and have proven effective in a variety of situations. However, limiting use to bait stations can greatly reduce the ability of users to establish the bait in some locations where the rodents are more likely to encounter and consume it and practical field efficacy of the available rodenticides will be likely be reduced. Also, limiting the choice of bait formulation to bait blocks reduces the ability of the user to select a formulation best suited for a particular environment; e.g., locations where familiar pellets would have greater acceptance than a novel bait block. In some situations the bait blocks are more appropriate because of moisture or other factors.

The Panel believed that EPA may have underestimated the complexity of effective commensal rodent control in the home and assumed that a one-size fits all approach will provide homeowners with satisfactory results. The requirement that rodenticides sold to residential consumers not contain the active ingredients brodifacoum, difethialone, bromadiolone, or difenacoum has the potential for increasing rodenticide resistance and limiting effective options. The Panel concluded that the EPA has not adequately considered the costs from increased rodenticide resistance and the potential costs associated with limiting chemicals that can be used in future products.

Charge Question 11 *- Are conforming rodenticide products containing the active ingredients warfarin, diphacinone, chlorophacinone, or bromethalin, along with non-chemical rodent control methods available to consumers and other options, capable of providing effective control of commensal rodents? Please provide the basis for your conclusions.*

For the near term, the Panel believed effective control is possible with a combination of both an effective product and non-chemical methods. However, for the long term, limiting chemical control options to only two classes of rodenticides will likely lead to an increase in the number of commensal rodent populations that exhibit anticoagulant resistance and that will further limit control options. It was the Panel's observation that the EPA has failed to recognize the difficulty associated with non-chemical control, especially in those communities where rodent populations are at high levels. The complexity of the physical environment, coupled with

food availability and the lack of what many would consider basic sanitation makes it impossible to effectively reduce harborage, eliminate food sources, manage adjacent land areas, limit access to buildings, or trap enough animals to impact the population. Dependence on non-chemical controls would be least effective for those neighborhoods that have the most significant problems. Further, many mechanical control products may not be as effective as chemical rodenticides.

The Panel concluded that the estimated added costs associated with the use of conforming rodenticide products along with non-chemical control are underestimated in the NOIC. The NOIC assumes that, on average, the cost is manageable and that the costs associated with homeowner initiated rodent control are comparable across all economic classes. With roof rats as a possible exception, commensal rodent infestations tend to be more significant and have a greater impact on neighborhoods that are considered impoverished. As a result of poorly maintained buildings, lack of appropriate levels of sanitation, and higher human population densities, the control of commensal rodents in low income neighborhoods is much more difficult. Those at or below the poverty level have greater commensal rodent control challenges and are the least able to afford to do something about it.

DETAILED PANEL DELIBERATIONS AND RESPONSE TO CHARGE

Charge Question 1: *Does the Agency's analysis of the mammalian toxicity studies and human incident reports provide a reasonable basis for concluding that exposure to warfarin, brodifacoum, difethialone and/or bromethalin can cause health effects in individuals who ingest these rodenticides? Are the adverse effects described in the children's incident reports [e.g., anemia, melena (bloody stool), hematemesis (vomiting of blood)], credible consequences of exposure to these active ingredients? Please provide the basis for your conclusions.*

The Panel believed that the mammalian toxicity studies provide a reasonable basis for concluding that exposure to warfarin, brodifacoum, difethialone and bromethalin can cause health effects in people who ingest these rodenticides. The commonalities in the physiology among mammals, including the laboratory rodents and humans, indicate that there are common targets for these toxicants. It is possible for adverse health effects to result if a sufficiently large ingestion occurs. This is true for any substance. The question that surfaces is whether humans are able to ingest a large enough dose to cause harm from an existing product that does not conform to the 2008 risk mitigation measures? The bulk of rodenticide exposures in humans occur as ingestions by children between 18 months and 36 months of age. Ingestions by young children are exploratory and sloppy in nature. Available data indicate that such exposures typically do not cause harm, and life-threatening effects or death are extremely rare. Exposures in older children and adults are typically intentional and often surpass the dose threshold for causing harm.

There is no question about the ability of anticoagulant rodenticides (including warfarin, brodifacoum and difethialone) to inhibit the action of vitamin K epoxide reductase which results in a decrease in the body's ability to clot blood. This anticoagulant action can cause effects such as prolonged clotting time, easy bruising and bleeding from mucous membranes. This is unlikely to occur in children that ingest less than 1 mg of active ingredient (20 grams dry weight at 0.005%). These effects are dose-dependent and have a slow clinical progression. Available evidence suggests that the vast majority of exposures to first and second generation anticoagulant rodenticide products by young children will not result in a clinically significant coagulopathy or bleeding. However, if the toxic threshold is exceeded, there is a widely available laboratory test and an antidote (vitamin K_1) with which clinicians are familiar because of therapeutic use of warfarin.

The toxic dose threshold for second generation anticoagulant rodenticides (SGARs) in children is believed to be approximately 1 mg of active ingredient. This corresponds to 20 grams of 0.005% bait or roughly 70% of a one ounce pellet bait pack or a one ounce bait block. A possible unintended consequence of switching from pellets to bait blocks in tamper resistant packaging is that ingestions become less common, but adverse effects are more likely when they do occur due to an increase of dose ingested per exposure. If a block is swallowed, the entire dose is administered at once, while for baits in pellet form, many pellets must be ingested to get an equivalent dose. EPA is encouraged to monitor for this issue and choking hazards associated with bait blocks.

Bromethalin is not an anticoagulant and is not expected to produce bleeding complications. Instead, it is a metabolic poison that disrupts oxidative phosphorylation in the mitochondria, which leads to increased sodium inside neurons. (However, it was pointed out by the Panel that the apparent specificity of bromethalin for the nervous system is somewhat surprising because classic uncouplers of oxidative phosphorylation frequently have more widespread effects within the body; bromethalin's mechanism of toxicity may not be fully understood at this point.) Clinically, this results in swelling of the brain (cerebral edema). As the swelling increases, neurologic effects will worsen and can ultimately lead to death. Bromethalin exposures are less well described in incident reports and in the open literature than anticoagulant rodenticide exposures. This is probably the result of the smaller market share observed with bromethalin-containing products. Only one death has been reported in conjunction with human exposure to bromethalin. This case was reported to involve the intentional ingestion of eight 21-gram packs (approximately 17 mg or 0.33 mg/kg of bromethalin) followed by progressive worsening of neurologic symptoms consistent with cerebral edema which resulted in death seven days post exposure. In general, severe bromethalin poisonings are very concerning for clinicians because of less human experience with them and, unlike the anticoagulants, there is no specific diagnostic test or antidote. Available data indicate exposures among young children typically involve small amounts and have benign outcomes. No information on the subchronic or chronic effects of bromethalin, or on toxicity to the developing central nervous system (CNS) was provided in the EPA documents, thus there is uncertainty regarding the health effects of low level subchronic and chronic bromethalin exposures, as well as the effects of bromethalin exposure during the early stages of life. Given that bromethalin targets the CNS and interferes with mitochondrial function, there is concern that the developing brain of young children may be particularly susceptible to the neurotoxic effects of bromethalin. Observations that mitochondrial dysfunction is often a prominent and early event in neurodegenerative diseases similarly adds to these concerns regarding the limited amount of toxicity information available on bromethalin (Cannon and Greenamyre, 2011).

Charge Question 2: *The human incident report summarizes a number of data and information sources used in the analyses and reviews conducted. Based on the incident report analysis, EPA has concluded that there are a large number of rodenticide exposure incidents that involve children less than 6 years old. While exposure generally results in no clinical harm to children, the exposures to rodenticides have the potential to result in severe outcomes and/or require medical care or follow-up. Does the SAP concur with the EPA's conclusions regarding the extent of exposures, potential severity of effects, and degree of risks posed to humans? Are the conclusions reached reasonably supported by the data analysis? Please explain the basis of your position.*

Panel Response: Incident reports provide important information because they reflect potential exposures and adverse consequences in humans who are accidentally exposed to toxicants, including the subject rodenticides, and, therefore, the incident reports should not be ignored. However, the incident reports should be viewed with a great deal of caution. The incident data come from several sources, all of which have strengths and limitations. Similarly, each source has its own unique and nuanced vocabulary, definitions and reporting criteria. Understanding these differences is important. Within these data sources many of the reports lack objective confirmation of ingestion. The terms "exposure" and "incident" only indicate that rodenticide

ingestion may have occurred. Hence, for most incident reports, accurate measures of true ingestions are lacking. These uncertainties can go in either direction—under-reporting of exposures, as EPA suspects, but also over-reporting of exposures that may not truly be exposures at all or may be exposures to levels that are not of any toxicological consequence. Certainly exposures to rodenticides have the potential to result in severe outcomes that would require medical care or follow-up. However, there appears to be relatively little data included in the incident reports that verify that exposures to people, including children, have occurred that were of a magnitude considered to be major incidents.

It is clear that EPA has demonstrated hazard and that there is risk, but the NOIC does not establish a quantitative level of risk for severe outcomes and, hence, it is difficult to concur with EPA's "degree of risks" posed to humans. It would be expected that an estimate of degree of risk would at least provide an indication of the expected likelihood of a severe outcome. An example given by one Panel member is that roughly 125 children less than 6 years old experience mild to moderate medical outcomes each year due to exposure to rodenticides. This would be one estimate of the numerator in a risk estimate. The denominator could be the total number of children less than 6 years old in the U.S., approximately 23.1 million in 2008, producing an estimate of 5.5×10^{-6}. But, if exposures are largely observed in children in low income families, the denominator could be smaller resulting in a higher estimate of risk.

Based on the available data, the Panel agreed with the EPA's assertion that exposure generally results in no clinical harm to children. While the possibility of harm exists, toxicity rarely occurs except in the setting of intentional ingestions or malicious poisoning. This relatively low risk to humans needs to be carefully weighed against the risks associated with poor rodent control.

One Panel member stated that it is important to reduce the opportunity for children to be exposed to these acutely toxic rodenticides. They pointed out that data show a considerable number of unintentional human exposures to rodenticides occur as a result of residential consumer use, and that children under the age of 6 are a large percentage of those exposed. This conclusion is supported by EPA's analysis of incident data from the American Association of Poison Control Centers (AAPCC) database which indicated that about 1% of the reported rodenticide exposures to children resulted in a medical outcome classified as either minor, moderate, or major. Information provided in public comments by the New York City Department of Health and Mental Hygiene (NYC DOHMH) also supports the conclusion. One third (n = 4,250) of the unintentional exposures to pesticides reported to NYC DOHMH's Poison Control Center between 2000 and 2010 were found to be exposures to rodenticides. Seventy-nine percent of these rodenticide exposures were to children under the age of 6, and 96% of these occurred in callers' homes. Moreover, NYC DOHMH found that 29% of these reports of rodenticide exposures to children under 6 involved exposures to products covered by the EPA's 2011 draft NOIC. The NYC DOHMH further noted that during the years 2000-2009, 82 New York City residents were admitted to hospitals because of severe and unintentional rodenticide exposures, and 57% of these individuals were children under the age of 6. These types of incidents have the potential for serious outcomes as the acute toxic effects associated with exposures to these rodenticides are potentially severe, and can include death.

The EPA's 2008 RMD and 2011 draft NOIC aim to reduce exposures of children and others to rodenticides used in commensal rodent control, thereby reducing the risks to human health posed by rodenticide use and the Panel member pointed out that the focus of the RMD and draft NOIC on reducing children's exposures to rodenticides is consistent with the EPA's efforts to protect children's health by taking into account behavioral, physiologic, and other differences between children and adults that can result in higher exposures to children, as well as increased susceptibility to adverse health effects associated with those exposures. The Panel member also stated that the RMD and draft NOIC are consistent with the EPA's Children's Health Protection Advisory Committee's recommendation that the Agency take actions to reduce children's exposures to chemicals with toxicity concerns (http://yosemite.epa.gov/ochp/ochpweb.nsf/content/Chemical_Criteria_Letter.htm).

The Panel member noted public comments provided by the NYC DOHMH that stated that proper rodent control requires integrated pest management (IPM). This entails removal of food sources that attract rodents and addressing structural features of the home to prevent access (e.g., sealing potential rodent entry points such as cracks and holes), in addition to the use of rodenticides and/or other means to clear the home of rodents. The draft NOIC indicates that the majority of residential consumers employ mechanical methods of rodent control, not rodenticides. Thus, not only are rodenticides not the sole tool for commensal rodent control, neither are they the primary tool employed by consumers.

Charge Question 3: *Based on the human incident report, EPA concludes that the use of conforming rodenticide products will reduce the risk rodenticides pose to humans by reducing the opportunity for exposure. Is it reasonable to expect that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of humans to commensal rodenticide products? Please provide the basis for your conclusions.*

Panel Response: The Panel stated that it is reasonable to expect that limiting consumer use to conforming rodenticide products, if used according to the product labeling, will generally reduce the opportunity for exposure of humans to these particular rodenticides because of the restricted ability to contact the baits. If the bait stations are not used correctly, then exposure to the rodenticides is still likely and adverse effects may occur. EPA is urged to give further consideration to the likelihood that consumers will not use the bait stations for all the rodenticides placed in their homes. There is concern that the potential additional expense of providing enough bait stations or the inconvenience of loading the bait stations might preclude consumer adherence to label directions regarding proper rodenticide application.

The data presented by EPA demonstrate that exposure generally results in no observable harm. Health outcomes associated with rodenticide exposures are better than those associated with numerous other pesticides and common household products. Poor health outcomes associated with unintentional rodenticide exposures in children are rarely observed and any reduction of outcome rates would, therefore, be modest. The Panel was not provided with all of the information relevant to the complete risk/benefit assessment of these rodenticides, and the Panel understands that the assessment of some public health issues related to the presence of rodents and use of rodenticides is currently being undertaken by another federal agency. While not within the charge questions to the Panel, the Panel urged EPA to make certain that a

thorough and well-researched assessment of the public health issues associated with a lack of rodent control (e.g., the potential for increases in rodent-borne diseases, bites) is provided by the Department of Health and Human Services (DHHS), and that this assessment be used in the overall risk assessment of the rodenticide products under consideration in this NOIC. Also, EPA is urged to make certain that rodent control can be adequately maintained for protection of human health following the proposed cancellations.

One of the concerns associated with exposure is cost to society. This was not specifically mentioned in the Charge Question but was part of the conclusions in the tier II review of human incidents document. The supporting data presented are not sufficient to draw conclusions regarding how RMD compliance would provide a benefit related to the societal costs. Any effect on utilization of emergency medical resources (poison centers, 911/pre-hospital emergency medical services (EMS) or emergency departments) in this age group is uncertain. It is also important to note that since 2007, U.S. poison centers have adopted a treatment guideline for anticoagulant rodenticides that discourages routine referral to health care facilities and laboratory studies for typical exposures in young children (Caravati, 2007). While many poison centers had already adopted this approach prior to this guideline being published, the effect of it on reducing health care facility utilization may not be fully captured in the 1999-2009 data that were reviewed.

Conforming packaging is likely to have less of an impact regarding exposures among adults and older children which are typically intentional in nature. Exposure rates in these groups are already very low but account for the vast majority of severe effects and deaths. They are less likely to be deterred by conforming packaging which may be subverted by breaking open the packaging/block or simply selecting a different poison. Hence, emergency medical resource utilization will likely be little changed in these groups. Selecting an alternative poison may affect clinical outcomes and resource utilization for better or worse depending on the substance selected.

Limiting consumer use to conforming products (i.e., bait stations) is expected to make it more difficult for children to come in contact with the rodenticide. Public comments and early market data submitted by Bell Laboratories, Inc., from calls made to the emergency medical advice line SafetyCall International on company products, suggest that human incident reports have decreased for post-mitigation compliant rodenticides, compared to pre-mitigation compliant products for comparable time periods. While encouraging, this trend has not been analyzed for significance.

Also, the use of bait blocks rather than bait pellets or powder is expected to make it less likely that rodents will carry bait out of the bait station and into areas where children can come in contact with it.

One Panel member expressed a concern about bait block size and the potential for choking if they are not used in conjunction with a bait station per product labeling.

Charge Question 4: *The pet incident report summarizes a number of data and information sources used in the analyses and reviews conducted. The EPA concludes that there is a high frequency of reported pet incidents involving rodenticides, many of which result in severe outcomes; this conclusion is further supported by the information reported in the open literature as well as the characterization of primary acute risk. Does the SAP concur with EPA's conclusions of the risks posed to pets by non-conforming rodenticide products? Are the conclusions reached reasonably supported by the data analysis? Please explain the basis of your position.*

Panel Response: The Panel interpreted the Charge Question as requesting a "yes" or "no" answer based on the available information. Thus, the Panel concurred that the results from the database searches and literature provided by EPA and others support the conclusion that exposure to, and adverse effects from, rodenticides, including anticoagulant rodenticides, have occurred in pets in the United States from 1999 to 2010. However, the Panel's response provides only the risk perspective, and does not include the benefit perspective of the analysis. The database results and literature review were interpreted as observational data, not an assessment of risk, *per se*; consequently, they do not support use of the terms "risk" or "high frequency" in the NOIC, at least to the extent that those terms imply that a risk assessment was conducted.

Recent evidence for numerous incidents involving pets and non-conforming rodenticides appears to be adequate and brodifacoum use in and around the home has been involved in the majority of the reports. Decreasing over-the-counter availability of brodifacoum is likely to reduce adverse pet events associated with it, if properly applied. The potential consequences of increased use of the non-anticoagulant rodenticide bromethalin are unknown. This is additionally worrisome due to current apparent consumer market popularity of bromethalin as the only non-anticoagulant rodenticide registered for homeowner use, and its high potential for causing severe clinical signs. These concerns are further compounded by the fact that there are neither readily available pre- or postmortem diagnostic tests for bromethalin, nor effective treatment options for severely intoxicated pet animals. Data from the Office of Pesticide Programs' Incident Data System (IDS) for domestic animal fatalities involving rodenticides for 1999-2009, rank bromethalin third after brodifacoum and bromadiolone. Animal Poison Control Center (APCC) data rank bromethalin as the second most likely rodenticide (between bromadiolone and brodifacoum) to result in a call.

Even though the number of calls is not equivalent to number of exposures, it may appropriately reflect the presence of these products in pet-owning households. National Pesticide Information Center (NPIC) data for domestic animal rodenticide exposures between 1999 and 2010 indicate that non-anticoagulant rodenticide exposures to products such as bromethalin are already increasing, though data show that this may be primarily driven by the use of zinc phosphide instead (see Figure 6 of EPA background document, "Rodenticides: Tier 2 Pet Incident Report in Support of NOIC").

A risk not mentioned in the NOIC is the increased risk of a choking hazard due to complete phasing out of non-block formulations in favor of block-only products. An additional risk not mentioned is the increase in risk of adverse effects due to exposure to a 1 ounce

(approximately 28 g) block when exposure in the data and information provided may have been exposure to less than 1 ounce; this is particularly relevant to pets with a small body weight. Another risk not mentioned in the NOIC is the increased risk of gastrointestinal trauma (e.g., foreign body gastroenteritis) due to ingestion of bait stations by pets, particularly dogs.

Charge Question 5: *The pet analysis has relied on the assessment of risks to wildlife from primary exposure as one line of evidence to characterize primary acute risk to pets from non-conforming rodenticide products. Is it reasonable to conclude that risks to pets are similar to risks to non-target mammalian wildlife, assuming comparable exposures? Please explain the basis of your conclusions.*

Panel Response: The Panel agreed that, to the extent that the mechanisms of action (inhibition of "recycling" of vitamin K_1, uncoupling oxidative phosphorylation, and increased circulating 25-hydroxy cholecalciferol causing hypercalcemia) is the same in pet and other non-target mammals, it is reasonable to conclude that hazards to pets and other non-target mammals are similar, but not the same.

The literature supports the notion that the "toxic dose" on a mg/kg body weight basis varies among mammals, so the term "comparable" must account for this dose difference in order to arrive at comparable risk. For the rodenticides under review, published experimental studies provide information on dose levels that produce adverse outcomes in dogs, cats, and, in some instances, other pets. Use of this pet-specific data may be more appropriate than extrapolation of risk from non-target mammalian wildlife. Based on the available wildlife data there is sufficient evidence that significant risks also exist for larger pets, as risk quotients (RQs) were found to increase with the body weight of the assessed generic/wild animal, though the potential risks to pets could be better evaluated by reviewing the available data that are specific for companion animal species. Pet-specific information would also better address potential differences in sensitivity among species and between different rodenticides.

The Panel stated that it is generally reasonable to conclude that risks to pets are similar to risks to non-target mammalian wildlife of comparable body sizes; however, the mammalian body weight groups of 15, 35, and 1,000 grams used to assess primary exposure risk are not practical for pets except in the case of the very smallest pets. The 1,000 and 3,000-gram size mammalian classes included in the secondary exposure risk assessment provide a better approximation of small dogs and cats, but not larger pets.

Charge Question 6: *Based on the pet incident report, EPA concludes that the use of conforming rodenticide products will reduce the opportunity for exposure of pets to rodenticides. Is it reasonable to expect that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of pets to commensal rodenticide products? Please provide the basis for your conclusions.*

Panel Response: The Panel did not agree with EPA that limiting consumer use to conforming rodenticide products will generally reduce the opportunity for exposure of pets to commensal rodenticide products. They concluded that the pet incident reports demonstrate that residential consumers in general do not read and/or follow label directions for current rodenticides and

hence, would not be any more likely to do this for rodenticide products formulated in block form. To the extent that conforming rodenticide products are provided outside of bait stations, the pet incident report does not support the conclusion that the opportunity for exposure of pets to commensal rodenticide products is likely to be reduced.

If conforming rodenticides are provided solely in tamper-proof bait stations that do, in fact, reduce exposure to dogs and other pets, the above conclusion may change. However, implementation of an approach of providing conforming rodenticides solely in tamper-proof bait stations is reasonably likely to increase cost, reduce benefit, and may give rise to additional risk not considered in the data and information provided.

Second generation anticoagulant rodenticides (SGARs) appear to be responsible for the majority of incidents involving pets. Since many of the reported pet incidents appear to involve pelleted and other loose bait forms, the use of conforming products can be expected to reduce, but not completely eliminate, exposures of pet animals to rodenticides. Use of rodenticides in bait stations will likely reduce the ease of accessibility and decrease the number of exposures involving pets, but use of them will not completely eliminate exposures, especially with dogs. Since the majority of the consumer market consisted of non-conforming products when the available data were collected, continued monitoring of incident data will be needed in order to evaluate the degree of effectiveness of conforming products, particularly bait stations and their durability, in reducing exposures of pets to rodenticides.

Charge Question 7: *The EPA has conducted a deterministic risk assessment to evaluate the risks of acute toxicity to non-target mammals and birds from primary exposure to non-conforming rodenticide products. In its assessment, EPA calculated risk quotients on an acute oral dose and acute dietary exposure basis for birds and mammals and further characterized the opportunity for exposure at lethal levels based on factors including the number of days required to feed and the mass of pesticide required to be consumed to reach lethal thresholds. Using the best available data, EPA made assumptions relative to toxicity, accumulation, and clearance of the pesticides that are material to the exposure and effects modeling in the deterministic primary risk assessment.*

a. Please comment on the reasonableness of the following aspects of EPA's primary exposure deterministic risk assessment:

- *Selection of toxicity endpoints for species common to all assessed chemicals in light of the incomplete overlap across available data sets;*
- *The use of allometric toxicity scaling approaches for birds;*
- *The reliance on mammalian first order liver or plasma elimination half lives to estimate whole body wildlife (birds and mammals) elimination rates for anticoagulants and bromethalin, respectively;*
- *The use of the time required and the consumption of rodenticide mass required to reach lethal thresholds as a means of comparing the relative risks of acute mortality following consumption of rodenticide bait.*

Panel Response:

- *Selection of toxicity endpoints for species common to all assessed chemicals in light of the incomplete overlap across available data sets.*

The EPA used data that were principally derived from standardized acute oral and dietary avian and mammalian toxicity tests. The principal endpoint in these tests is death, and the risk from primary exposure was evaluated by "calculating dose-based or dietary-based risk quotients (RQs)". An RQ of 1 indicates that the exposure (dose or concentration) is equal to the selected toxicity value (i.e., LD_{50} or LC_{50}). The RQ is compared to the EPA's level of concern (LOC) which is 0.5 for non-listed species and 0.1 for threatened or listed species. This deterministic methodology has a long history of use and is acceptable for a screening level risk assessment. The primary exposure assessment is a worst case scenario as it assumes that the diet consumed is exclusively bait containing the rodenticide.

Death is used as an endpoint as it is definitive, and regulatory requirements have resulted in the generation of such data for the test compounds in question. Regrettably, data for other adverse outcomes (e.g., overt signs of toxicity, frank bleeding, bruising, hematomas, coagulopathy, histopathological lesions, and other sublethal measures related to the mechanism of action, or impending death) are not available for all of the compounds in question, and their significance is more challenging to interpret.

In contrast to the Agency's selection of uniform species, a better approach would be to conduct chemical-specific assessments with conceptual models that identify receptors of interest for a refined risk assessment. The receptors should include target commensal rodents and non-target birds and mammals (i.e., species identified in incident reports that are exposed and/or poisoned by ingesting bait) (see Figures 1 and 2 below). A screening level ecological risk assessment was already conducted in 2004. A continuation of this deterministic metric that was conducted in 2004 has only provided limited improvements with regard to the uncertainty discussed in the prior assessment. If time constraints dictated a more limited screening assessment, the Agency should consider requiring the registrant to provide a refined assessment for each compound with a clear conceptual model identifying specific receptors of interest and uncertainty factors where data gaps occur. For example, there are clearly enough data for a species sensitivity distribution for several compounds. There are seven data points for avian LC_{50}s for warfarin which could allow an LC_{50} determination (with uncertainty analysis). For the other less data rich compounds, 10-fold safety factors could be used with the lowest value. For mammalian acute dose LD_{50}s, the LD_{50} value used for the RQ appears to be highly subjective as the lowest rat values are used when clearly several values are less than the rat values for brodifacoum, difenthialone, chlorophacinone, diphacinone and bromethalin. Other species appear to be much more sensitive and significant variability is evident in the data sets. A species sensitivity distribution would provide a more quantitative approach which could provide a quantitative estimate of uncertainty. The current approach is likely to underestimate risk to more sensitive species. For some groups of toxicants, bobwhite quail and mallards are remarkably tolerant. Birds of prey are more sensitive to anticoagulant rodenticides than bobwhite and mallards (Rattner et al. 2010, 2011a; Watanabe et al, 2010). However, it is unlikely that birds of prey would directly consume bait, and may only encounter small quantities of undigested bait in the gastrointestinal tract of prey. Since the LOC for the SGARs brodifacoum and difethialone is exceeded in less sensitive test species (e.g., quail, mallards), the decision to restrict SGARs based on these data will likely protect more sensitive wildlife species.

Figure 1. Primary exposure conceptual model to target species

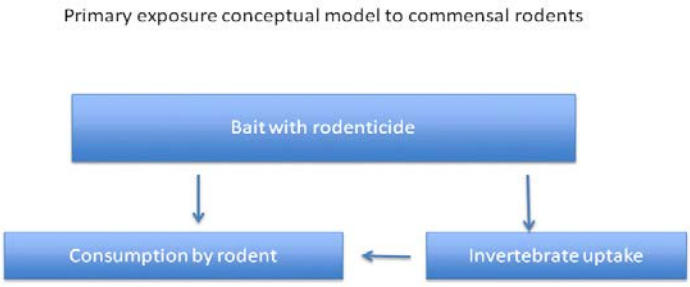
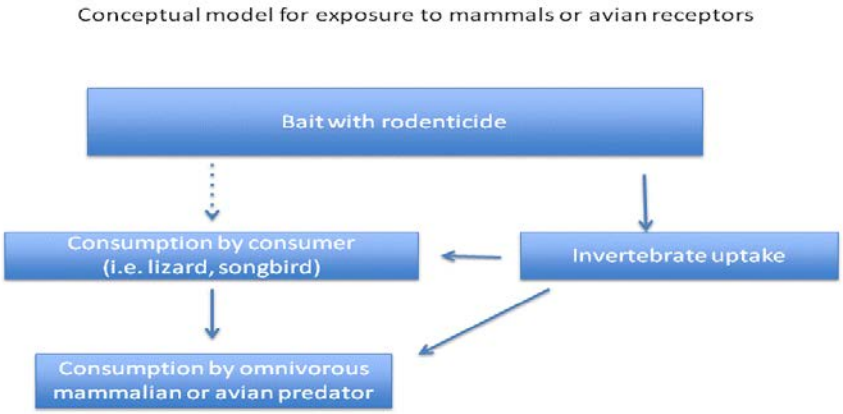


Figure 2. Conceptual model for non-target exposure avian and mammalian wildlife



A problem in the analysis of the FGARs (i.e., chlorophacinone, diphacinone) is the exposure scheme used in the avian and mammalian acute oral toxicity tests. A single oral dose or multiple doses are administered in a 24-hour period. However, as described in the EPA background document, "Efficacy Issues Regarding Control of Commensal Rodents in the U.S. Using Registered Rodenticides" (page 14), FGARs require multiple feedings, and the toxicity of these compounds increases by nearly two orders of magnitude when the dose is administered for 5 days (Ashton et al., 1986). Similar findings have been observed in controlled exposure studies in non-target raptors (Rattner et al., 2011b, 2011c). Acute oral toxicity tests for FGARs may greatly underestimate toxicity, and a paper describing this issue in wildlife species is in press (Vyas and Rattner, 2012). The inclusion of LC_{50} test data in the risk analysis (Table 4-7 in EPA's White Paper ("Risks of Non-compliant Rodenticides to Non-target Wildlife") partially addresses this concern, and the LOC for chlorophacinone is actually exceeded.

A recent controlled exposure study was conducted in which graded doses of the FGAR diphacinone (up to 22.6 ppm) were fed to eastern screech-owls for 7 days (Rattner et al., 2011c). Food consumption was measured in this study. Coagulopathy and anemia were observed at ingested doses of 0.24 mg diphacinone/kg owl/day. Lethality (2 of 5 owls) was observed at greater daily doses, with the most sensitive individual dying following consumption of 0.82 mg diphacinone/kg owl/day. Ingestion of diphacinone bait (50 ppm active ingredient – Table 4-7, EPA White Paper) by a more sensitive species (e.g., owl) actually exceeds the LOC (RQ = 2.21), but owls are not primary consumers; this issue will be further addressed in the Panel's response to Charge Question 8.

The risk assessment does not address hazard to reptiles and other species, which may consume bait in temperate regions of the United States. This issue is being investigated by scientists at the USDA National Wildlife Research Center in Fort Collins, CO.

- *The use of allometric toxicity scaling approaches for birds.*

The use of allometric toxicity scaling in birds is generally reasonable and warranted, and the rationale is explained by Mineau et al. (1996, 2001). The use of allometric scaling in birds is also well-accepted in the field of avian medicine for the calculation of drug dosages given the lack of pharmacokinetic data for therapeutics for most avian species. In lieu of direct data for each species of concern, allometric scaling is the best available approach to address metabolic differences among birds of different sizes and taxonomic groups. However, caution must be used in estimating LD_{50} values for very large or very small bird species, or birds for taxonomic groups that are poorly represented in their base dataset (Mineau et al., 2001). Notably, hawk and owl species seem to be more sensitive to some groups of compounds (cholinesterase-inhibiting pesticides) than would be predicted by scaling factors (Mineau et al., 1999). As members of the orders Falconiformes (hawks) and Strigiformes (owls) are non-target species frequently affected in rodenticide secondary poisoning incidents, development of chemical specific extrapolation factors and/or additional empirical toxicity data for these species would improve the risk assessment.

While allometric scaling is necessary for this deterministic assessment due to data gaps, the Agency should consider pursuing physiologically-based pharmacokinetic (PBPK) models that estimate dose within predators following oral exposure. Clearly, species differences exist between birds and mammals in biotransformation and other dispositional factors (e.g., quantity of plasma protein binding).

- *The reliance on mammalian first order liver or plasma elimination half lives to estimate whole body wildlife (birds and mammals) elimination rates for anticoagulants and bromethalin, respectively.*

For the anticoagulant rodenticides, the use of first order liver elimination half-life is a reasonable approach for the initial estimation of whole body elimination rates, given the issues and limitations discussed in the EPA White Paper. The liver is known to be a site of storage for these compounds in both mammals and birds (Huckle et al., 1988, 1989). However, data are available for coumarin anticoagulant rodenticides' biphasic elimination which may occur at some dose levels (Vandenbroucke et al. 2008). A preliminary estimate of the hepatic diphacinone clearance in kestrels orally dosed with 50 mg/kg suggests an overall half-life of 22 hours, with an initial phase (6 to 48 hours post-dose) half-life of 7.8 hours and terminal phase (48 to 168 hours post-dose) half-life of 59.8 hours (Horak, personal communication as described in Rattner et al., 2011a). These data suggest that diphacinone is cleared more rapidly in kestrels than in rats and pigs.

For some drugs and toxicants, half-life and whole body elimination rates differ considerably among species of birds, and can have serious consequences (e.g., effects of nonsteroidal anti-inflammatory drugs in several species of wild birds, and in particular, diclofenac that devastated populations of old world vultures but appear to be relatively non-hazardous to new world vultures and some other raptors). Predictions of xenobiotic clearance (hepatic or renal) by use of avian and mammalian extrapolation and scaling factors has been examined for a number of drugs, and the prediction error is much lower when avian data are used

to predict xenobiotic clearance in birds (Hunter et al., 2008). Again, it was unclear to the Panel why a probabilistic approach was not used to quantify liver concentrations of individual compounds. Only one study in rats was used in the accumulation calculations. The rationale for using one study was not clear. Sufficient data were available for a probabilistic measurement for brodifacoum. For the other compounds, specific safety factors could be used when data were not present and this approach would have provided a more quantitative assessment. In addition, first order assumptions likely underestimate clearance, since a two compartment model appears to be more realistic. The Panel recommended that the Agency pursue development and use of PBPK models to estimate levels in the liver of primary and secondary consumers following oral exposure. Clearly, species differences exist in biotransformation and pharmacodynamic factors in avian species when compared to mammals.

As discussed in the EPA White Paper, first order kinetic assumptions likely underestimate clearance, but the assumption of whole animal consumption by predators probably provides some conservatism for the uncertainty of this assumption. Additional conservatism is also needed to account for plasma protein binding by the anticoagulants, particularly for mammals, but perhaps less so for birds with plasma that has less albumin and, presumably, lower binding capacity. In fact, it is somewhat misleading to conclude that bioavailability is solely derived from dietary consumption or uptake. Free compound is required to interact with the target enzyme (epoxide reductase) for the anticoagulants.

While there are no data on elimination half-life of bromethalin in liver, its half-life in blood plasma of rats is 5.6 days. It is suggested that this non-anticoagulant rodenticide is rapidly eliminated from the body. However, it is possible that using plasma elimination half-life will underestimate whole body elimination rate.

- *The use of the time required and the consumption of rodenticide mass required to reach lethal thresholds as a means of comparing the relative risks of acute mortality following consumption of rodenticide bait.*

This scenario assumes that non-target species consume only bait. This is a worst case exposure scenario, and highly conservative. Primary bait ingestion of high potency rodenticides (i.e., requiring consumption of less mass) yield large RQs (body burden:LD_{50} ratios), and pose the greatest risk to non-target birds (Tables 4-3, 4-4, and 4-7 of EPA White Paper; Appendix Tables B-1, B-2, and B-3). The calculated RQs for SGARs and bromethalin for birds are large, and these baits might evoke toxicity and lethality with a single day exposure. Even warfarin bait poses a significant hazard to a small passerine exposed for just 1 day. With exposure durations of greater than 1 day (Tables 4-3, 4-4, and 4-7 of EPA White Paper; Appendix Tables B-2 and B-3), the likelihood of SGARs, bromethalin and even FGARs evoking lethality increases. As non-target primary consumers are less likely to feed exclusively on rodenticide bait in lieu of natural food items, compounds that do not provide a lethal dose in a single feeding should pose less risk. For non-target mammals (Tables 4-5, 4-6 and 4-8 of EPA White Paper; Appendix Tables B-4, B-5 and B-6), all of the formulations are hazardous and could possibly evoke lethality if consumed for as little as 1 day.

The EPA White Paper, and the conceptual model shown on page 29, discuss invertebrates as a possible source of exposure to compounds. The relative contribution to dietary exposure is uncertain, but given the incident report of the Philadelphia Zoo, invertebrate trophic transfer to insectivorous species may be significant, especially in rural and agricultural applications. Fisher et al. (2010) discuss the consumption of rodenticide bait and the accumulation of brodifacoum and diphacinone in terrestrial invertebrates. The calculation of bioaccumulation factors (BAFs) within invertebrates and other prey items for each compound should reduce uncertainties of exposure to wildlife.

b. In addition, does the Panel concur with EPA's analysis and conclusion that use of non-conforming rodenticide products (i.e., not in bait stations) can cause adverse effects to non-target wildlife? Please provide a basis for your conclusions.

Panel Response: The Panel did concur with EPA's analysis and conclusion that use of non-conforming rodenticide products can cause adverse effects to non-target wildlife. Direct consumption of rodenticide bait appears to be responsible for death of non-target wildlife species in rural and urban/suburban settings that may be related to homeowner use. Overall, 8 primary exposure incidents were reported for wild birds (Table 7-2, EPA White Paper) and 57 incidents for wild mammals (Table 7-4, EPA White Paper). In the highly probable certainty index, there were 25 incidents for brodifacoum (Table 6-1, EPA White Paper), 1 incident for chlorophacinone (Table 6-6, EPA White Paper), and 3 incidents for diphacinone (Table 6-7, EPA White Paper). Bait in the form of pellets or forms otherwise not contained within a bait station undoubtedly enhance the likelihood of ingestion by non-target primary consumers. In turn, the more primary consumers that contain residues, the more widespread contamination of the food chain will be through secondary and possibly tertiary exposures in predators and scavengers.

c. Is it reasonable to expect that placing rodenticide products in tamper resistant bait stations with formulations expected to remain in the bait station will generally reduce the opportunity for primary exposure of wildlife to commensal rodent control products? Please provide a basis for your conclusions.

Panel Response: The Panel believed it is reasonable to expect that placing rodenticide products in tamper resistant bait stations, with formulations expected to remain in the bait station, will generally reduce opportunities for primary exposure of wildlife. Bait stations will reduce the likelihood of wildlife (e.g., grey squirrels, chipmunks, passerine birds) accessing the bait. While the possibility of bait access exists for small non-target mammals and birds, this mitigation measure should reduce the risk of primary poisoning in many species of non-target wildlife. However, care should be taken to determine the impact of invertebrate access, bioaccumulation and subsequent consumption by mammals and birds.

Charge Question 8: *The EPA has conducted a deterministic risk assessment to evaluate risks of acute toxicity to non-target mammals and birds from secondary exposure to non-conforming rodenticide products. In its exposure estimate, EPA used both calculated theoretical contamination levels in prey and available empirical data. EPA also characterized the secondary exposure risk using secondary feeding studies and factors including the number of contaminated animals required to be consumed to reach lethal exposure thresholds. For these analyses, using the best available data, EPA made assumptions relative to toxicity, accumulation, and clearance of the pesticide that are material to the exposure and effects modeling in the deterministic secondary exposure risk assessment.*

a. Please comment on the reasonableness of the following aspects of EPA's secondary exposure deterministic risk assessment:

- *The use of theoretical body burden calculation together with empirical whole body residue data to produce a reasonable range of estimated exposures for secondary exposure pathways;*
- *The use of the number of prey items required to reach lethal thresholds as a means of comparing the relative risks across the assessed rodenticides of acute mortality following consumption of contaminated prey;*
- *The conclusion that the results of predator / scavenger feeding studies are consistent with the findings of the deterministic secondary risk assessment;*
- *The use of a standardized set of avian toxicity endpoints (i.e., species tested across all the assessed chemicals) in light of information on diphacinone suggesting that raptors may be more sensitive than the surrogate avian species used in the risk assessment.*

Panel Response:

- *The use of theoretical body burden calculation together with empirical whole body residue data to produce a reasonable range of estimated exposures for secondary exposure pathways.*

Based on existing data, and given that there are many uncertainties in determining body burden in prey species (e.g., species differences in sensitivities to rodenticides, elimination rates, actual prey feeding behavior in field situations, prey rodenticide residues, assumption that 100% of rodenticide in carcasses is bioavailable, assumption that predators eat only contaminated carcasses), the methods/approach used in the EPA's risk assessment are generally appropriate for this problem. The shortcomings in this assessment are inherent in the data available and the associated uncertainties. However, in spite of these concerns, the RQs calculated from theoretical data and empirical residue data are consistent among rodenticides. The overall weight of the available evidence supports the Agency's conclusions even considering the well addressed uncertainties in Section 5.4 of the assessment.

- *The use of the number of prey items required to reach lethal thresholds as a means of comparing the relative risks across the assessed rodenticides of acute mortality following consumption of contaminated prey.*

Many wildlife species that are potential secondary consumers of rodenticides maintain territories or home ranges within which they hunt. If an animal is consistently hunting in an area where rodenticides are in use, the consumption of multiple contaminated prey items is very likely. Therefore, the Panel believed that assessing risk in terms of number of contaminated prey items ingested is a reasonable approach.

For avian secondary consumers, given that the standard test species (quail and mallards) are potentially less sensitive to anticoagulant rodenticides than birds of prey (Rattner, 2011a; Watanabe et al., 2010), a group of birds commonly reported to suffer anticoagulant rodenticide toxicosis, a level of uncertainty exists in this assessment. Some predators preferentially consume certain organs and tissues which could increase or decrease total rodenticide intake. Owls regurgitate significant portions of their prey items and up to 25% of the rodenticide dose/residue contained within those prey items (Eadsforth et al., 1991; Newton et al., 1994).

For the SGARs brodifacoum and difethialone, a 1,000 g bird (such as a red-tailed hawk) could consume a lethal dose of 2 or 4 mice, respectively (as given in Table 5-10 for 1 day accumulation) with 1 to 2 hunting events. Even if the 2 or 4 poisoned mice were not consumed on the same day, given the persistence of SGARs within the liver and the potential for cumulative toxicity (Eason et al., 1999), the LD_{50} could still be reached. For larger prey items (e.g., Norway rat) the number of prey ingested that would result in the LD_{50} is less than 1 at both the 1 day and 6 day accumulation levels. As the LD_{50} is derived from species that are likely less sensitive than birds of prey, this line of evidence supports the conclusion of high risk to avian predators from SGARs.

For FGARs, given the potentially higher sensitivity of birds of prey and the unknown sensitivities of other birds, the calculated number of prey items needed to reach the LD_{50} may be overestimated. Also unknown is the effect of repeated exposure to FGARs in birds of prey. The conclusion of a relatively lower risk of FGARs to predatory birds is based on incomplete data and is a major source of uncertainty.

There is also uncertainty regarding the risk of secondary toxicity of bromethalin, as tissue retention of this chemical is unknown. If cumulative toxicity in birds is possible with bromethalin, this chemical may pose a risk to avian predators/scavengers, as a 1,000 g bird of prey can consume 6 to 16 mice (as given in Table 5-10 of the EPA White Paper for 3 day and 1 day accumulation, respectively) or 1 to 3 rats or similar sized prey (as given in Table 5-11 of the EPA White Paper for 3 day and 1 day accumulation, respectively) over the course of days to weeks. A similar scenario could be expected to occur with mammalian predators/scavengers.

- *The conclusion that the results of predator/scavenger feeding studies are consistent with the findings of the deterministic secondary risk assessment.*

While, as noted in the EPA White Paper, it is not possible to determine the exact amounts of rodenticides fed to the study subjects in each case, it is clear from these studies that brodifacoum, in particular, poses a significant secondary hazard. However, while the overall secondary risk assessment determined a lower risk to avian predators/scavengers from diphacinone and chlorophacinone, this lower risk from consumption of FGARs by birds of prey is not well supported by the cited feeding studies and does not match the deterministic predictions in Table 5-5 of the EPA White Paper**.** One study cited in the EPA White Paper (Table 5-19: Observed Effects of Chlorophacinone on Birds Consuming Contaminated Carcasses) found that all exposed American kestrels showed signs of chlorophacinone poisoning (Radvanyi et al., 1988). Likewise, the EPA White Paper (Table 5-20: Observed Effects of Diphacinone on Birds Consuming Contaminated Carcasses) cites two studies showing death in great horned and saw-whet owls (Mendenhall and Pank, 1980) and signs of diphacinone toxicosis in golden eagles (Savarie and LaVoie, 1979). While the EPA's assessment of the kestrel and golden eagle studies showed that they support a decreased risk associated with chlorophacinone and diphacinone because the birds did not die, all birds did, in fact, show signs of bleeding in a laboratory setting. Even though all study birds recovered, survival would not be as likely in wild birds and equivalent adverse effects could be expected at much lower levels of FGARs. The Panel suggested EPA reassess the significance of these studies.

Feeding studies, in general, are more likely to underestimate than overestimate effects of all anticoagulant rodenticides in wild birds and mammals for two reasons. First, predators/scavengers in the wild may be exposed to contaminated prey for longer time periods than in the studies, allowing for greater accumulation of the rodenticide, dependent on the rate of elimination for each chemical in a given species. Second, animals in the wild are subjected to far more physical stress than animals maintained in a laboratory, allowing greater opportunities for trauma and subsequent bleeding to occur. Levels of anticoagulant rodenticides that do not lead to overt hemorrhage at rest may prevent normal coagulation in response to minor trauma. Thus, animals in the wild may suffer signs of anticoagulant rodenticide poisoning or death with the same dose of anticoagulant rodenticide at which laboratory-maintained animals do not. Excessive bleeding from minor wounds is seen commonly in wild birds of prey suffering from anticoagulant rodenticide toxicosis (Murray and Tseng, 2008: Stone et al., 2003). Following this line of reasoning, even relatively low-level anticoagulant rodenticide exposures could result in increased morbidity and mortality in wildlife species, both avian and mammalian, in association with more severe injuries such as those sustained in collisions with motor vehicles and fights with conspecifics.

- *The use of a standardized set of avian toxicity endpoints (i.e., species tested across all the assessed chemicals) in light of information on diphacinone suggesting that raptors may be more sensitive than the surrogate avian species used in the risk assessment.*

Regarding the conclusions that SGARs present a high risk to secondary consumers such as raptors, the Panel believed the decision to restrict the use of SGARs is warranted given that

the standard test species used are indeed likely to be less sensitive than raptors and that the LOC was exceeded for the test species.

Regarding conclusions that FGARs present less risk than SGARs to birds of prey in particular, the use of standardized avian toxicity endpoints is problematic as certain raptor species have been shown to be more sensitive than the test species. Using data on diphacinone in screech-owls, as described in the Panel's response to Charge Question 7a (Rattner et al., 2011c), RQs for diphacinone might be exceeded. Notably, results from Acute Dose-Based RQs for Secondary Birds (Section 5.1.1.1 and Tables 5-5 and 5-6 of EPA White Paper) using LD_{50} estimates suggest low risk for chlorophacinone and diphacinone, while empirical data in Tables 5-19 and 5-20 of the EPA White Paper suggest otherwise. In addition, two studies (Watanabe et al., 2010: Rattner et al., 2011a) showing that some owls (great horned owls, snowy owls) and American kestrels are more sensitive to the FGARs warfarin and diphacinone, respectively. Reliance on standardized avian toxicity endpoints using less sensitive species is likely to underestimate the risk to birds of prey from both FGARs and SGARs making it difficult to determine if FGARs present less risk than SGARs to birds of prey.

b. Does the Panel concur with EPA's analysis and conclusion that consumption of living or dead rodents poisoned by brodifacoum or difethialone presents a greater opportunity for adverse effects to non-target wildlife compared with the rodenticides warfarin, diphacinone, chlorophacinone, or bromethalin? Please provide a basis for your conclusions. Does the Panel concur that cancellation of products containing brodifacoum and difethialone sold to residential consumers will reduce the opportunity for secondary exposure for wildlife to rodenticides? Please provide a basis for your conclusions.

Panel Response: In response to the first part of the Charge Question, the Panel believed EPA's background paper presented a thorough review of the existing literature on these rodenticides and detailed evaluations of theoretical and empirical models of prey rodenticide burdens and feeding scenarios. The case for a high risk to non-target wildlife from brodifacoum exposure is well supported. The conclusions that FGARs and bromethalin present a lesser risk to non-target wildlife, particularly birds of prey, may be flawed due to the reliance on test species that may have lower sensitivities to FGARs than birds of prey, and due to limited information on tissue persistence of bromethalin. Incident data (cited on EPA White Paper pages 135 and 136) and feeding studies (Savarie et al., 1979; Mendenhall and Pank, 1980; Radvanyi et al, 1988) have shown that secondary toxicity from diphacinone and chlorophacinone has occurred in birds of prey. In addition, it is not clear that brodifacoum and difethialone should be considered together since their overall risks are not similar. Based on the results of secondary feeding studies there appears to be a significantly lower risk associated with difethialone.

The Panel also re-emphasized its concerns about bromethalin. Given the nonspecific neurologic signs that intoxicated animals may display and considering the similarities of these signs to common injuries seen in wildlife presented to veterinarians and rehabilitation centers (e.g., head trauma), cases of bromethalin intoxication could be easily overlooked. The lack of characteristic signs of bromethalin toxicosis on post-mortem examination will also complicate detection. This assumption seems to be supported by a lack of reported incidents involving

wildlife. Bromethalin intoxications are very difficult to diagnose, detect, and treat, and there is not enough evidence to support its suggested use as a lower-risk alternative to SGARs.

The cancellation of products containing SGARs would probably reduce the overall opportunity for secondary exposures involving wildlife; however, more research is needed to determine the risks of difethialone and potentially increased exposures of non-target wildlife to FGARs and bromethalin. In general, the analysis presented by the EPA did not include real numerical quantifications of risk, and there seems to be a great degree of uncertainty for some components of the risk assessment. While these uncertainties can be better addressed in the case of brodifacoum, where more data are available, the application of some uncertainty/safety factors would be needed for the other compounds under consideration.

Regarding the second part of the Charge Question, the incident data and exposure data (sections 6.1 and 6.2 of EPA White Paper) provide strong evidence that SGAR use, particularly brodifacoum, in urban and suburban areas has the potential to impact non-target wildlife, and that brodifacoum contamination of the terrestrial food chain is widespread. Use of rodenticide products containing brodifacoum by residential and commercial consumers is extremely likely in urban and suburban areas. The reasoning that, since brodifacoum has no registered field uses, residential use is responsible for the extent of exposure among wildlife, is sound. In a study of birds of prey presented to a wildlife clinic in central Massachusetts, 86% of 161 birds of prey were positive for anticoagulant rodenticide residues (Murray, 2011). Ninety-nine percent of positive birds were found to have brodifacoum residues in liver tissue. No birds were found to have chlorophacinone, diphacinone, or warfarin residues. The study area included predominantly suburban and urban areas, which would indicate that residential or commercial use of brodifacoum is responsible for the widespread exposure found. For these reasons, it can be reasonably assumed that cancellation of products containing brodifacoum for residential use should decrease the contamination of the food chain with this rodenticide which poses a high risk of mortality to secondary consumers.

The path of SGARs through the food chain is unknown. That is, the contribution to food chain contamination of commensal rodents, non-target small rodents, larger primary consumers (such as squirrels) and insects is not understood. What would be helpful would be critical lethal body burden data for animals directly consuming rodenticide products followed by percentages of this burden that is then transferred to the carnivore eating exposed prey. Whether professional use of SGARs will continue to facilitate entry of these chemicals into the food chain cannot be determined at this time; hence, continued evaluation of the risk of SGARs to non-target secondary consumers should be continued. However, as noted in the EPA background paper, the use of integrated pest management is the best approach for decreasing the reliance on rodenticides. Unknown is the extent to which risk to secondary consumers, and birds of prey in particular, may increase if residential use of chlorophacinone, diphacinone, and bromethalin increases.

Charge Question 9: *Incident data demonstrate that rodenticide use can result in wildlife mortality, and that such wildlife mortalities occur in urban and suburban areas. Based on this incident data, EPA has concluded that consumer use of rodenticides in urban and suburban areas may be a significant contributor to the wildlife mortalities attributable to rodenticides. The EPA also determined that both primary and secondary poisonings have been documented.*

a. As part of its analysis of incidents, EPA analyzed the available incident data in order to associate incidents with specific land use categories, i.e., agricultural, urban, suburban areas. In performing this analysis, EPA relied on the information in incident reports identifying associated habitat or on the address reported for the incident and then used remote sensing information to assign a land use category with the incident. Please comment on the reasonableness of this approach to using location information to support the conclusion that use of the commensal rodenticides addressed in the draft NOIC causes wildlife mortalities in urban and suburban areas, as well as rural areas.

Panel Response: The issue at hand and the focus of this SAP is the cancellation of domestic/household use of certain rodenticide products. It seems reasonable to assume that use of these domestic products to control commensal rodents would be greater in areas with dense populations of people. However, rodenticides are also deployed by professionals representing commercial and institutional entities in urban and suburban areas and it is not clear how one would separate domestic from commercial/institutional usage as sources in urban and suburban land use areas.

At issue is the extent to which wildlife co-existing in urban and suburban land use areas experience increased risk of exposure to and poisoning by the products listed in the NOIC. EPA addressed this issue by sorting the incidents of rodenticide-linked wildlife poisonings into land use categories based on the density of human development. The Agency used data primarily from the Ecological Incident Information System (EIIS) database. The data came predominantly from state governments (mainly New York and California) and a few incidents reported by pesticide registrants. The Agency made an effort to cross reference data with other available databases on pesticide effects on wildlife (section 6.1.2 of the EPA White Paper).

The incidents in the database were classified using a certainty index to determine the likelihood that a specific compound was the cause of observed adverse effects. The certainty index ranges from “unlikely” to “highly probable” and classification was made either by the attending wildlife pathologist or later by EPA staff using the available information. The Agency further classified the exposure ‘type’ of each incident into ‘primary’ or ‘secondary’. Primary involves direct consumption of rodenticide bait by an animal. Secondary involves consumption by predation or scavenging by an animal of other animals which have directly consumed rodenticide product.

Designation as primary ‘P’ or secondary ‘S’ was based mainly on diet preferences (e.g., raptors, such as hawks and owls, are most likely to have been exposed to rodenticides through predation or scavenging on primary exposed animals). Species such as squirrels, being largely herbivores, were most likely exposed from feeding directly on bait, and were classified as primary exposures or ‘P’. For omnivores such as corvid birds or mammals such as raccoons,

primary or secondary poisoning was determined where possible on the basis of necropsy results, and, in particular, whether the gastrointestinal tract contained bait remains (primary) or animal tissues (secondary).

The incidents were then classified spatially as being from urban, suburban or rural environments, based on information about where the animal was found, as provided in the database. The majority of reported incidents were linked to brodifacoum, and the evidence was quite compelling. The ratio of urban/suburban to rural incidents of primary brodifacoum poisoning was 34:4 (33:3 in probable or highly probable category). The ratio of urban/suburban to rural incidents for secondary poisoning by brodifacoum was 97:50 (90:45 in probable or highly probable categories). Thus, the overall total for primary and secondary in all categories was 131:54.

The evidence for a small number of incidents for the other SGAR compound, difethialone, are consistent with those of brodifacoum. The five primary and secondary classified incidents were all in urban/suburban environments. A small number of incidents were also reported for warfarin, bromethalin, chlorophacinone and diphacinone, but no clear spatial trends were evident for those compounds.

The data in the incident reporting system should be considered in light of the potential for various sources of uncertainty. Such factors include the accuracy of the diagnosis of anticoagulant poisoning as opposed to other causes of death. Uncertainty also comes from issues such as variation in carcass condition at time of autopsy, in turn related to many factors based on time on ground, weather conditions, storage conditions (e.g., fresh, refrigerated, frozen); the experience of the veterinary pathologist in encountering anticoagulant poisoning; and the analytical chemistry accounting for factors such as variation among laboratories in methods, quality assurance, etc. It is possible, therefore, given these uncertainties, that some diagnoses of anticoagulant poisoning were incorrect. But it is also possible that, for example for animals found dead and stored frozen for some time, some diagnoses were missed, particularly if the wildlife pathologist preferred to err on the side of caution and classify suspected poisonings as unknowns. However, there is no reason to believe that the incidence of incorrect diagnoses should be related to the habitat category and, therefore, significantly bias the results of the spatial analysis. Thus the trends among habitat types should not be particularly biased. Again, those trends are not minor; they vary from 10:1 for primary to 2:1 for secondary to 131:54 for the total. Although not analyzed statistically, it seems unlikely that such large differences would occur by chance alone.

Another source of error or uncertainty comes from possible variation in the likelihood of a carcass being found and reported between urban/suburban and rural areas. It could be argued that surveillance would be greater in an area of more dense human populations, and inhabitants might be more likely to pick up a dead raptor or report a dead bobcat. However, in a rural setting, wildlife mortality from domestic use rodenticides is still likely to occur near a farm or rural residence. With the necessary close connection to their land and what goes on there, farmers or rural residents may still notice and collect or report wildlife carcasses, at least of birds of prey.

There is a variety of other uncertainties related to the finding of carcasses and the incidence of total mortalities. The number reported is likely only a small portion of the actual mortalities, including poisonings by rodenticides or other toxicants, given that raptors can carry prey to roost sites, which, in case of owls will likely be more secluded. Given the slow time to death, raptors may further seek cover as their condition deteriorates. Carcasses are quickly scavenged in most environments. Many field experiments support this finding, and some are cited in the EPA White Paper. The potential of an impacted bird being hit by a vehicle and the carcass being severely damaged, and, therefore, less likely to be picked up, is also probably greater in urbanized areas with greater vehicle traffic.

The EPA further supported their spatial analysis of incident reporting by analyzing data from New York and California separately by plotting primary and secondary incidents on maps of population density. The majority of reported incidents occurred in areas of increased population density.

It should be noted that a further source of error or bias in the land use component of this analysis may come from changes in land use with time, particularly increased urbanization. It appears that the designation of land use for the spatial analysis was based on current or at least recent status. The database extends over the period from 1980 to 2011, although the bulk of the records are over a ten year period from 1994 to 2004, during which some changes in land use probably occurred. It is possible, therefore, that some incidents which were classified as urban or suburban based on current land use, occurred when the land was still in rural use at the time of the incident.

The analysis was further supported by a review of published literature from the U.S. and other countries. Those published reports were generally in agreement with the analysis of the EIIS data, which include some of the incidents also reported in the literature, in that brodifacoum was overwhelmingly the compound associated with non-target wildlife mortality, both primary and secondary, and that there were consistent trends of more reported SGAR-related mortalities in urbanized environments.

The Agency further examined the reports of exposure based on chemical analysis of rodenticide residues in livers of animals found dead or which died or were euthanized after being found in a distressed state. Clearly, the SGARs, in particular, are becoming widespread contaminants in food chains of birds of prey and other predators. To date, there are few comprehensive analyses of spatial trends in this relatively novel phenomenon. The majority of samples of predatory birds and mammals analyzed from urban areas of North America contained detectable residues of one or more SGAR compounds (Albert et al., 2010: Lima and Salmon, 2010; Murray, 2011). This is presumably due to their persistence and capacity to accumulate in liver tissues. SGARs are almost behaving like persistent organic pollutants (POPs) such as the polychlorinated biphenyls (PCBs) or the persistent organochlorine insecticides. It should be noted that there are very limited data on possible toxicological implications of long term chronic exposure, including issues such as developmental effects on young animals.

Of further relevance to this assessment are data on diet and habitat use of three owl species inhabiting urbanized environments in south western British Columbia, the barn owl (*Tyto*

alba) and of diet of two other species, the barred owl (*Strix varia*) and the great horned owl (*Bubo virginianus*). Although these data are unpublished, they were recently presented and abstracted by Hindmarch and Elliott (2011a, 2011b) and the Panel was informed of the results for these deliberations.

In more urbanized environments (classified by standard GIS methods, GME 2011), using radio-telemetry methods in the field, barn owls in Greater Vancouver and neighboring suburbs foraged mainly in grassy strips adjacent to highways, railways and buildings where there was greater potential to encounter commensal rodents, particularly rats. Based on data from regurgitated pellets, a standard method for examining diet of owl species, barn owls ate a variety of prey, with 15 different species found in the 2,701 pellets collected during this study. In a total of 6,225 individual prey remains identified, voles (primarily field voles, *Microtus townsendi*) were the main prey item, regardless of the amount of urbanization within their home range. However, Norway rats were present in the diet and there was considerable variation among sites in the proportion of rats consumed by barn owls (range: 0-37%). The consumption of rats appeared to coincide with increased urbanization, as there was a significant correlation between the proportion of rats in the diet and an index of urbanization (Kendall's Tau = 0.46, $p > 0.01$, $R^2 = 0.21$). It is also interesting to note that when sites were categorized based on the amount of urbanization (Category 1: 0, Category 2: 0-33%, Category 3: 33-64%, Category 4: > 64%), house mice, although very few in total, were found (n = 15). Eighty percent of mice in pellets were found at sites in two latter categories, urbanized to highly urbanized sites.

It should be noted that these results contrast with one of the few studies that looked at the diet of owls in relation to rodenticide exposure (Hegdal and Blaskiewicz, 1984). However, that study was conducted in a relatively rural environment where owls had the option of foraging in farm fields in search of preferred vole (*Microtus spp*) prey. For great horned and barred owls, location and identification of pellets can be more challenging. However, diets were compared for the larger species from five urbanized and five rural settings. From those pellets, 551 prey items were identified from 17 different prey species. The presence of rats in the diet varied among sites from virtually 0.01% to as high as 76%. There was a positive relationship with increased urbanization, although the result was non-significant (Kendall's Tau = 0.44, $p = 0.095$, $R^2 = 0.19$). This could, in part, be attributed to heteroscedastic data and a small sample size; the study is ongoing.

The average mass of rats consumed by barn owls was 73.8 ± 37.2 gram (n = 282), which is considerably smaller than that of barred and great horned owls (116 ± 65.0 gram, n = 73). However, the mode for the two groups was the same (mass = 60 gram), but the prey size distribution for barred and great horned owls is more skewed to the right, toward larger prey, which accounts for the disparate means. That may indicate that the optimal prey size is similar for both groups, but that the barn owls, due to their smaller size, have a narrower prey size distribution and less able to handle larger prey. The modal mass fits within the size distribution of field voles (40-60 gram, Nagorsen, 2005), supporting the notion that barn owls are vole specialists and that size is an important factor in prey foraging decisions made by barn owls (Fast and Ambrose, 1976; Derting and Cranford, 1989).

In summary, for both groups of owls there is a positive association between the consumption of rats and increased urbanization, where at the extreme end, rats made up a large proportion of the diet. This suggests that there is an increased risk that these three owl species could be exposed to prey contaminated by rodenticides in more urban areas. In addition, the data show that great horned and barred owls consume on average a greater number of larger rats in their diet than barn owls, which infers that there is a greater risk of secondary rodenticide poisoning posed to these two owl species, supported by published data on inter-specific presence of SGARs in liver tissue (Albert et al., 2010).

Given the reports of grey squirrel primary poisonings by SGARs in the EIIS database and elsewhere, the Panel anticipated some proportion of squirrels in the diet of the urban owls, and that was a potential explanation for the reported poisonings of barred and great horned owls in Vancouver and neighboring suburban areas, and the high incidence and concentrations of SGAR residues in the liver of those species (Albert et al., 2010). However, only two squirrel remains were found in the diet of these owls. That may be, in large part, due to diurnal habits of squirrels versus the largely nocturnal hunting habits of the owl species. The initial conclusions from this study are that the larger *Bubo* and *Strix* species inhabiting urban areas consume a substantial, but varying, proportion of rats in their diet and thus, are at risk of exposure to rodenticides. Owls inhabiting more urban environments appear to be at greater risk of exposure to SGARs than those in more rural environments. Similarly, the smaller and more specialist *Tyto* owls consumed fewer rats and rats of small size classes, but, nonetheless, they do eat rats and some house mice, and the proportion increases with urbanization of their foraging habitat.

The Panel found no other North American diet studies on either great horned or barred owls which included urban habitat. There are, however, data for the great horned owl ecological equivalent, the eagle owl, *Bubo bubo*, from southern and eastern Europe. Norway rats made up 35% of the diet of eagle owls in a city in Romania (Sandor and Ionesco, 2009). In a long-term study of 25 eagle owl nests in suburban and lowland agricultural habitats in Italy, Norway rats constituted 25% of the diet (Marchesi et al., 2002). A small diet study conducted in the city of Hurghada, Egypt on desert eagle owls (*Bubo ascalaphus*), showed that house mice and Norway rats comprised 78.1% of the prey remnants and 89.1% of the consumed biomass (Sandor and Moldovan, 2010).

These data seem to support the idea that there is, indeed, a complete exposure pathway for secondary poisoning of avian predators, at least for owls, from application of rodenticides and the species of primary exposure is the targeted Norway rat. This exposure pathway likely accounts for a proportion of the wildlife incidents and for reports of hepatic SGAR residues reported from urban/suburban environments.

Of relevance to the above point, both avian and mammalian predators appear to be increasingly adapting to urban and suburban environments. In the case of avian predators, there has been a well documented recovery of many populations as residues of DDT and related legacy organic contaminants have declined in ecosystems across North America and elsewhere, combined with reductions in persecution. Those raptor populations have returned to habitats that are increasingly fragmented and urbanized, particularly in high quality coastal, estuarine and riperian environments. Species such as the peregrine falcon (*Falco peregrinus*) and Cooper's

hawks (*Accipiter cooperii*) take advantage of nesting structures in cities, and are attracted to feed on birds with close associations with humans, such as house sparrows, starlings and dove species (Boal and Mannan, 1999; Park et al., 2010). Populations of those raptors inhabiting urban environments are also contaminated to a greater degree than rural counterparts by persistent organic pollutant chemicals such as the polybrominated diphenyl ether (PBDE) flame retardants (Newsome et al., 2010; Elliott et al., 2010).

b. EPA analyzed the available incident data in order to differentiate primary and secondary wildlife mortality. For this analysis, EPA relied on information on the dietary requirements of the moribund species and any identified gut contents when available. Does the Panel find this approach a reasonable way to evaluate the occurrence of primary and secondary toxicity as causes of wildlife mortality? Please provide the basis for your conclusions.

Panel Response: Separating wildlife mortality incidents caused by rodenticide exposure into primary and secondary events based on knowledge of dietary preferences is a reasonable approach, but caution must be used when relying on the presence of any identified gut contents in omnivorous species.

Incidents involving birds of prey can be almost exclusively categorized as secondary poisoning. Owls, for example, are predators adapted to and focused on catching live prey, particularly ground dwelling species such as rodents. Most species of diurnal raptors such as hawks, falcons and eagles, are primarily predators, but will resort to scavenging if live prey are not available or during periods of weather related stress. Bald eagles will readily scavenge and some individuals likely prefer to scavenge. Regardless, it is highly improbable that any of the raptor species would feed on bait pellets or blocks.

Mammalian predators and scavengers, such as wild felids or mustelids, are most likely to be exposed secondarily through predation or scavenging, but could conceivably be attracted to and exposed through certain pellet or bait block formulations (e.g., those with fish scents/flavors) so categorizing them is more problematic. Wild canids, such as foxes and coyotes, fall within the omnivore category and could conceivably be exposed through consumption of contaminated insects, treated grains, pellets or bait blocks as well as being potentially exposed via predation or scavenging.

Species which are primarily herbivorous such as songbirds, squirrels and non-commensal rodents would be exposed to rodenticides almost exclusively through obtaining access to treated grain, pellets or bait blocks. Voles and other small wild rodents can inhabit vegetated areas adjacent to buildings, and potentially encounter and consume rodenticide baits. Grey squirrels are common residents of urban and suburban areas throughout North America. They readily forage at bird feeders, on pet food, and will chew into plastic garbage bins as well as food and animal feed containers. Thus, they would readily be expected to examine rodenticide bait stations and feed on crumbs or even shake and manipulate the stations in an attempt to access bait (J. Elliott, personal communication.). Ground feeding songbirds are known to enter bait stations and feed on bait blocks. Cavity nesting songbirds, in particular, may be at risk of primary exposure. Song sparrows (*Melospiza melodia*) have been found dead near bait stations with residues of brodifacoum in liver tissue. There is recorded video of house sparrows (*Passer*

domesticus) readily entering bait stations and feeding on unloaded bait blocks (J. Elliott personal communication.). There is a published account of songbirds (chaffinches, *Frinailla coelebs*) poisoned by an experimental application of the rodenticide, calciferol, in southern England, presumably by entering the bait stations to feed (Quy et al., 1995). The case of songbirds is further problematic as there is some potential of secondary exposure via feeding on invertebrates that fed directly on bait, or even tertiary exposure via necrophagus insects which fed on primarily poisoned rodents, but these vectors have not been well established (Howald, 1997).

Categorizing exposure to omnivorous species such as corvid birds, raccoons and opossums is more problematic. Crows and ravens, in particular, will capture live prey if available and could potentially take a moribund rodent. Also, they will readily scavenge and could be attracted to bait and bait stations. Ravens, in particular, have been known to manipulate bait stations during eradication programs on seabird islands and break into bait storage containers (Howald et al., 1999).

For omnivorous and/or scavenging species, due to the delayed onset of signs caused by anticoagulant rodenticides, analysis of stomach contents that are present at the time of the animal's death will not necessarily determine primary or secondary exposure. That is, absence of bait granules in the gastrointestinal tract at time of death does not rule out primary poisoning as the animal could have ingested the lethal dose 3 to 5 days earlier. Likewise, bait present in the gastrointestinal tract at the time of death may not have caused the animal's death, although it does show that the animal had access to bait and would ingest the bait. In this case, the presence of granules upon death can suggest that the animal may also have consumed a lethal feeding of bait several days prior to death, but it is not absolute proof of primary poisoning.

In summary, the Panel concluded that this approach of separating primary and secondary poisonings by diet is basically sound, but post-mortem evidence from gut contents must be interpreted with caution.

Charge Question 10: *EPA requires registrants of commensal rodent control products to demonstrate that their products meet criteria for efficacy. The registrants of conforming rodenticide products have submitted such data to EPA, and EPA has determined that their products meet these criteria. Do the meeting of these efficacy performance criteria and EPA's analysis of the effectiveness of conforming rodenticide products reasonably support conclusions that conforming rodenticide products provide effective options for chemical control of commensal rodents by nonprofessional users? If you conclude that conforming rodenticide products do not provide effective options for chemical control of commensal rodents by nonprofessional users, please discuss to what extent the following requirements affect the availability to consumers of effective options for control of commensal rodents:*

- *The requirement that rodenticides sold to residential consumers must include tamper-resistant bait stations;*
- *The requirement that rodenticides sold to residential consumers must be in forms (e.g. bait blocks) which are reasonably expected to remain within the bait station; and*
- *The requirement that rodenticides sold to residential consumers not contain the active ingredients brodifacoum, difethialone, bromadiolone, or difenacoum.*

Please provide the basis for your conclusions.

Panel Response: The Panel did not believe that efficacy data alone can be used to conclude that conforming rodenticide products are an effective option for the control of commensal rodents by nonprofessional users. The effectiveness of products vary greatly across species, populations, and time (Tobin et al., 1993; Witmer, 2007a and 2007b; Pitt et al., 2011). This variation has been demonstrated repeatedly with several of the conforming products. Prior rodenticide exposure and rodenticide resistance (via either genetic or behavioral changes) may account for some, but not all, of the variation in control effectiveness. Environmental realities, including but not limited to, access to areas where rodents are normally found, structural condition of the home or building, availability of alternate food sources, learned foraging behaviors, variation in wild strains and neophobia, all play a part in the effectiveness of a rodent control effort (Clapperton, 2006). It is not unreasonable to expect that certain rodenticides and rodenticide formulations perform better in one environment and are less effective in another environment.

Tamper resistant bait stations provide some increased level of safety and have proven effective in a variety of situations. However, limiting use to bait stations can greatly reduce the ability of users to establish the bait in some locations where the rodents are more likely to encounter and consume it and practical field efficacy of the available rodenticides will likely be reduced. Placing bait into small spaces such as inside of walls, under foundations, or in attic crawl spaces will be impractical with bait stations and/or larger bait blocks. In addition, placing baits in bait stations may decrease or delay uptake of bait by rodents, further reducing effectiveness, thereby allowing commensal rodents to continue to be a significant risk to human health (Buckle and Prescott, 2011). Especially with rats, time to acclimate to the bait stations and to begin consuming adequate bait to induce mortality will be delayed. Rodents may also avoid established bait stations that have been disturbed by predators.

Limiting the bait formulation reduces the opportunity to select the formulation that is best suited for the environment in which control efforts are taking place. In some cases, pellets will have greater acceptance than a novel bait block. In some situations the bait blocks are more appropriate because of moisture or other factors. The Panel believed that EPA may have underestimated the complexity of effective commensal rodent control in the home and assumed that a one-size-fits-all approach will provide homeowners with satisfactory results.

The requirement that rodenticides sold to residential consumers not contain the active ingredients brodifacoum, difethialone, bromadiolone, or difenacoum has the potential for increasing rodenticide resistance and limiting effective options. The Panel concluded that EPA has not adequately considered the risks and costs from potential rodenticide resistance and the costs associated with limiting chemicals that can be used in future products in the background document "Impact Assessment of the Draft Notice of Intent to Cancel Selected Residential Consumer Rodenticide Products to Control Commensal Rodents." The Panel recognized that the information available about rodenticide resistance is limited and dated making it difficult to quantify the potential impacts. However, even with the limited work done in the early 1980s, there is evidence of resistance to first generation rodenticides in many regions of the United States (Jackson et al., 1985). The increased use of first generation anticoagulants is likely to increase the potential for the development of populations that are resistant to these rodenticides (Rost et al., 2009; Berny, 2011). Although EPA recommended alternating rodenticides or using acute toxicants, most consumers will not review the available literature to make choices based on the potential of populations to develop resistance (see background document "Impact Assessment of the Draft Notice of Intent to Cancel Selected Residential Consumer Rodenticide Products to Control Commensal Rodents"). The body of science concerning rodenticide resistance and the understanding of the selection pressures that drive resistance in pest species suggest that significantly limiting the chemistry available for rodent control will speed the inevitable development of resistance (Pelz et al., 2005; Berny, 2011).

The number of conforming products will greatly reduce the potential options for consumers. Several of the alternative active ingredients, such as cholecalciferol and zinc phosphide, are not currently available to homeowners. With limited choices, consumers may have fewer effective products and effective products may not be available in all locations.

Appropriate use of bait stations is likely to improve the goal of limiting rodenticide exposure to children, but the impact could be difficult to measure. Health resource utilization (poison centers, calls to primary care providers, 911/emergency medical services, or emergency departments) in the setting of a potential rodenticide exposure in a child is largely driven by parental concern and fear rather than actual clinical need. A reasonable parent who finds their child around a poison (bait pack, station or block) and in a situation with a possible exposure (touching, licking or swallowing), often will not trust the resistant packaging and will utilize emergency medical resources out of caution and concern. Such cases can be effectively triaged away but still require the utilization of resources and will result in a reported exposure. Hence, reducing exposure risk does not result in a linear correlation with reduced health care utilization and reporting.

Charge Question 11: *Are conforming rodenticide products containing the active ingredients warfarin, diphacinone, chlorophacinone, or bromethalin, along with non-chemical rodent control methods available to consumers and other options, capable of providing effective control of commensal rodents? Please provide the basis for your conclusions.*

Panel Response: For the near term, the Panel believed effective control is possible with a combination of both an effective product and non-chemical methods. However, for the long term, limiting chemical control options to only two classes of rodenticides will likely lead to an increase in the number of commensal rodent populations that exhibit anticoagulant resistance and that will limit control options. The distribution of current anticoagulant resistant populations in the United States is not known. However, populations resistant to first generation anticoagulant rodenticides were widely distributed more than 30 years ago (Jackson et al., 1985). The likely increased use of first generation anticoagulants would be expected to hasten the development of resistant populations. The development of pesticide resistance is well understood and is understated in the NOIC discussion on second generation anticoagulant rodenticides (Berny, 2011).

The NOIC assumes that homeowners should rely more on non-chemical means of rodent control. The Panel is concerned that in the NOIC, EPA has failed to recognize the difficulties associated with non-chemical control, especially in those communities where rodent populations are at high levels. The complexity of the physical environment, coupled with food availability and the lack of what many would consider basic sanitation makes it impossible to effectively reduce harborage, eliminate food sources, manage adjacent land areas, limit access to buildings, or trap enough animals to impact the population (Advani, 1992; Witmer, 2007c). Dependence on non-chemical controls would be least effective for those neighborhoods that have the most significant problems. Further, many mechanical control products are not as effective as chemical rodenticides and mechanical tools are not subject to any efficacy requirements (Frantz and Padula, 1983; Shumake, 1997).

The Panel concluded that the estimated added costs associated with the use of conforming rodenticide products along with non-chemical control are underestimated in the NOIC. The NOIC makes the assumptions that, on average, the cost is manageable and that the costs associated with homeowner initiated rodent control are comparable across all economic classes. In reality, commensal rodent problems are not evenly distributed across income levels. With roof rats as a possible exception, commensal rodent infestations tend to be more significant and have a greater impact on neighborhoods that are considered impoverished. As a result of poorly maintained buildings, lack of appropriate levels of sanitation, and higher human population densities, the control of commensal rodents in low income neighborhoods is much more difficult. Those at or below the poverty level have greater commensal rodent control challenges and are the least able to afford to do something about it. Physical exclusion, managing surrounding areas, and enhanced sanitation are often not reasonable options. The potential decreased efficacy of first generation anticoagulants may further impact consumers. If the consumer selects a product to target a resistant rodent population or the population has decreased susceptibility, the cost to manage the infestation may greatly increase from the costs presented because additional applications and products would be required. The probability of consumers selecting ineffective products will increase if fewer active ingredients are available.

Use of commercial applicators or expecting the government to manage the rodent populations is not a viable option for many residents. Rodent infestations in many urban areas are an ongoing problem and not a single event. Thus, the costs of traps or rodenticides cannot be considered on a "per infestation basis" but have to be considered as an ongoing cost since individual efforts will seldom result in even the localized elimination of rodents. This should be considered a social equity issue.

Several members of the Panel expressed concern that noncompliance with product labeling is likely for a number of reasons and inappropriate use will continue, even with RMD compliant products. In order for the measures in the RMD to be effective, consumers must follow the product labeling.

Additional Panel Comments

Log P or LogK_{OW} Values

The Log P or LogK_{OW} of the rodenticides in the EPA White Paper should be reviewed and included as components of the analysis of the ecological risk assessment.

Potential Risks of Bromethalin

While the potential risks of bromethalin have been extensively discussed in regard to humans, pets, and wildlife, specifically regarding the secondary toxicity potential of this chemical in wildlife, there simply are no data. It should be noted that it is possible that bromethalin may not pose a secondary toxicity risk to predatory/scavenging wildlife if the parent compound or its metabolites do not retain activity after ingestion by the primary consumer. However, given the difficulty of detecting poisoning incidents from bromethalin in wildlife, research to determine the risk of secondary toxicity is urgently needed.

Brodifacoum Probabilistic Risk Assessment

A probabilistic assessment for brodifacoum was conducted in 2004 by Cadmus (Cadmus Group, 2004) and subsequently reviewed by the EPA (U.S. EPA, 2005). Assessments were focused exclusively on secondary exposure models to non-target predators and scavengers. The assumption was that primary exposure does not occur in non-target receptors of interest, which were primarily canids. EPA rightly concluded, that exposure to non-target receptors that have access to baited stations and consume contaminated prey would be dramatically reduced thus leading to the conclusions of diminished overall risk to brodifacoum. Additional limitations of the study included exposure relegated exclusively to Norway rats, use of exotic species in species sensitivity distributions, lack of small mammal and avian receptors of interest, omission of toxicity values less than the lowest dose, and pooling residue data, all of which could be relatively simple to correct.

Some of the mathematical calculations were also overly complex and not well described. The exposure model was described as:

DD = FIR x PD x PT x C, where;

DD = Daily dose
FIR = Food intake rate
PD = the percentage of rodents in the diet
PT = the percentage of rodents exposed to the pesticide
C = Concentration of pesticide in exposed rodents.

The variables for the equation are highly uncertain, particularly when this is limited to one prey item (rodents). PT would be virtually impossible to empirically confirm. In fact, based on the monitoring data provided, and given the persistence of brodifacoum, it is likely that all prey items, particularly in urban locations, are contaminated to a certain degree. It appeared that

PT was the critical factor for exposure assessment in the document and, hence, the most uncertain feature. FIR was based on a fairly complex set of additional variables, each with an additional degree of uncertainty.

A more direct approach might be to calculate an exposure value for each potential prey item with subsequent addition for total exposure. A prey item distribution for each receptor of interest in urban/suburban and rural locations could be used to provide an estimate for the percentage of each item to the total diet, and a distribution of residue values in each item (where available) could be used for C (without pooling) using half of the detection limit rather than zero. Based on comments made by other Panel members, prey data from gut contents are apparently available for some avian predators (owls, etc.) as well as canids. Appendix D from the EPA White Paper may also be mined to construct the distribution.

Alternatively, dietary bioaccumulation factors (deterministic) could be derived from empirical data for prey items in each setting (urban/suburban, rural) to estimate exposure. Similar approaches have been used for persistent organic pollutants (U.S. EPA, 2008). The final body burden concentration could be presented as a probabilistic distribution and compared to the species sensitivity distributions of North American mammalian and avian LD_{50} and LC_{50} values. If a threshold liver value could be determined, a higher degree of certainty could be applied. Each distribution could also undergo Bayesian and/or Monte Carlo analyses for uncertainty determinations.

Indoor versus Outdoor Use

Whether existing or new products are for 'indoor use only' versus 'indoor and outdoor' was not clear. Also, does 'outdoor' always mean 'within 50 feet of buildings'? This clearly has substantial implications for exposure of non-target wildlife. The designation of what is a building, and therefore, the extent of potential outdoor use was not clear.

Current labels that allow use outside of buildings imply that using these rodenticides as formulated for outdoors is safe. By adjusting the homeowner label to limit use of the available second generation rodenticides to indoors only would help the casual user understand these products are not appropriate for use outdoors and would allow the continued use of a broader range of formulations while potentially helping address wildlife exposure issues. This still has some limitations such as: 1) homeowners would only be able to manage commensal rodent problems before the rodents were inside the living area by using conforming rodenticides in bait stations and 2) this would not reduce the potential for human exposure. Setting aside the limitations, this potential label change would reduce the potential for target and non-target animals (including pets) that are outside of the home from being exposed to the rodenticides.

Commercial and Institutional Use Relative to Domestic/Household Use

The issue of commercial and institutional use relative to domestic/household use of products was not clear. It was difficult to determine the relative importance of the two types of use with regard to exposure of non-target wildlife. This problem was not discussed in the background documents. It is not clear whether regulation of domestic uses will significantly

reduce exposure of non-target wildlife if commercial and institutional use of SGARs, for example, will be continued, and is in fact at much greater scale. Among other points, it would be very useful to see data, if available, on the scale of usage of the rodenticide products under review between domestic and commercial applications.

Recognizing the need to not disclose confidential business information, data which may be useful, if offered by the registrant(s), in reducing uncertainty in the reasonable likelihood of reducing wildlife exposure (particularly secondary exposure) is disclosure of the percentage of rodenticide bait used by professional pest control operators and that used by residential consumers in one or more relevant urban and suburban areas (possibly defined by zip code).

Grouping all SGARs Together Regarding Hazard

Should all of the SGAR products be grouped together in the conclusion regarding their hazard? Perhaps alternate SGAR products, although highly toxic, are possibly less persistent and accumulative and may, therefore, pose a lower hazard to non-target wildlife. Such compounds may be less risky/hazardous alternatives to bromethalin.

Pest Resistance and Use of FGARs

The role of increased pest resistance from use of FGARs was not addressed in the background document. It was raised as an issue in the public comments, and there appears to be a valid concern. Evidence from Europe indicates that resistance to first generation anticoagulant rodenticides is widespread. Although evidence in the U.S. is extremely limited and quite old, it demonstrates that rodents with at least one gene associated with resistance in Europe are also present in the U.S. If increased usage of an FGAR alternative leads to development of widespread pest resistance, which appears to be the case in many countries, there appears to be a potential risk of needing to re-introduce SGARs, or other alternative products, back into the domestic market in 10 years or so. The presumption that sufficient first generation anticoagulant rodenticides and non-anticoagulant rodenticides will be both available and effective in a practical manner in the field, while reasonably anticipated, has not yet been substantiated, raising caution about the benefit portion of the equation.

Population Level Effects

There are no data to indicate population level effects on wildlife from homeowner uses of rodenticides in suburban and urban settings.

Rodenticide Use Awareness Programs

More proactive training and education as currently being carried out in the United Kingdom and Europe should also be considered. Helping homeowners more easily understand how their actions can impact children, pets, and wildlife has the potential of reducing the off label uses that increase risk of non-target impacts. It would be worth taking a closer look at the Campaign for Responsible Rodenticide Use to understand how that has impacted use of rodenticides in the United Kingdom. If there is evidence that programs such as the Campaign for

Responsible Rodenticide Use can reduce non-target impacts there may be value in considering a similar program in the United States.

Diagnosis and Treatment Costs of Non-Anticoagulant Rodenticide Exposure

A societal cost not sufficiently included in the data and information provided is the increased cost of diagnosis and treatment of pets, and perhaps other non-target species, exposed to non-anticoagulant rodenticides. Generally speaking the cost of treatment is higher, and the prognosis is lower, for the non-anticoagulant rodenticides compared to the anticoagulant rodenticides.

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