**Peer Review of EPA/OPP/EFED's "Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals"**

A previous draft of the rodenticide risk assessment was subjected to a formal peer review by Dr. Raymond O'Connor, Dr. Elwood Hill, and Dr. Charles Eason. The qualifications of these reviewers and their comments on the risk assessment are presented below. Agency comments have been inserted where appropriate in the reviews. The peer reviews were conducted on a previous draft of the assessment, and references to page numbers, table numbers, etc., may not correspond to those in the final document. Many revisions were made to the final risk assessment in response to the comments and suggestions of the peer reviewers.

Peer reviewers:

**Dr. Elwood Hill** has conducted research on wildlife toxicology since 1966 with the National Communicable Disease Center, Patuxent Wildlife Research Center and as a private contractor. He has published widely on the hazards of agricultural pesticides to wildlife, and on development and validation of wildlife testing protocols. Dr. Hill has routinely served as a toxicology consultant to the U.S. Fish and Wildlife Service, U.S. Environmental Protection Agency, various State environmental programs, and the private sector. On many occasions, he has been an ad hoc member of the U.S. Environmental Protection Agency's Scientific Advisory Panel (FIFRA) for issues from wildlife testing protocols and pesticide registration through development of probabilistic risk assessments. Dr. Hill is a long-standing member of the Society of Toxicology, a charter member of the Society of Environmental Toxicology and Chemistry, a Certified Wildlife Biologist, and has been an Adjunct Professor at the University of Maryland (Program in Toxicology) and the University of Nevada (Center for Environmental Sciences and Engineering).

**Dr. Raymond O'Connor** has been Professor of Wildlife Ecology at the University of Maine since 1987. His research has focused on the ecology of farmland birds (particularly in relation to pesticide use), on ecological indicators, on biodiversity modeling, and on the human dimensions of the environment. Dr. O'Connor has authored two books and more than 150 scientific papers and reports. He has been an invited member of numerous workshops and working groups, including meetings and Panels on the environmental risks of pesticides and their assessment organized by the U.S. Environmental Protection Agency Society, by the Environmental Toxicology and Chemistry, by National Audubon Society, and by NAFTA. He also has served widely as a consultant on bird population issues, including work for the U.S. Fish and Wildlife Service, U.S. EP, Canadian Wildlife Service, and for various non-governmental organizations and commercial firms.

**Dr Charles Eason** is Toxicologist and Research Team Leader of the Pest Control and Wildlife Toxicology Team and Environmental Health Programmes, Landcare Research New Zealand Ltd, He is co-founder of the Centre for Environmental Toxicology and team leader of the Pest Control and Wildlife Toxicology team. Dr. Eason has more than 10 years extensive research and practical experience in vertebrate pesticide toxicology and has published over 100 papers relating to the efficacy, safety, and comparative risks of vertebrate pesticides. He has received numerous awards, honors, and distinctions. His work includes assessment of the environmental impact of pesticides and contaminants, using novel techniques and providing novel improved toxicants, baits, and pest control strategies, toxicity testing of pesticides to minimize environmental and nontarget risks.

# EXTERNAL PEER REVIEW OF

# Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals

BY

**Elwood F. Hill, Ph.D.**

## INTRODUCTION

I have reviewed the subject risk assessment, found it to be quite thorough in evaluation of "acute" risk of rodenticides to birds and nontarget mammals, and strongly encourage the U.S. Environmental Protection Agency to continue development of quantitative techniques such as the "decision table" for use in risk assessments. The subject risk assessment was a comparison of nine rodenticides (including several modes of action) for reregistration rather than the unique review of a new product as normally conducted by the Agency. This approach added apparent complexity to the risk assessment that was ameliorated by development of the decision table in support of the Agency's risk presumption.

In this instance, the decision table was simplistic but adequate because the risk assessment was restricted to factors of acute toxicity, whether from primary or secondary exposure of birds and nontaget mammals. Clearly, development of decision tables for risk assessments involving other levels of toxicity (e.g., chronic, reproductive) and chemical fate and ecological factors will be more complicated, especially in regard to weighting the importance of relevant variables or even deciding which variables are critical for the evaluation. However, and of utmost importance, if the Agency chooses to pursue development of quantitative decision tables for use in risk assessment, it must avoid the temptation to over-value the "tool" at the expense of sound scientific judgment.

My overall impression of the risk assessment per the several questions you posed is found below. Detailed questions, comments and suggestions pertinent to the comparative risk assessment follow this section. Both the narrative and tables have been carefully reviewed and critiqued.

## GENERAL QUESTIONS (paraphrased):

***Question 1. Do available data and analysis support the risk conclusions?***

Yes. However, in addition to brodifacoum and difethialone, bromadiolone should be considered a high acute risk to nontarget animals regardless of its arbitrary rank as a "second option" (Table 7). In fact, bromadiolone is equally hazardous as a primary and secondary risk to nontarget mammals as are brodifacoum and difethialone (Table 1, Table 6). The question then becomes philosophical: Are wild birds and mammals of equal value? I suggest they are equal and all three of the above rodenticides should be considered acutely hazardous to homoiothemic vertebrates.

Another aspect of this question is the nature of the comparative risk assessment. Rodenticides are mostly used in areas inaccessible to most wildlife other than small mammals. Thus, primary acute toxicity, though the intended purpose of a rodenticide, is not usually an important risk factor for birds or most mammals. The main risk to these species is secondary toxicity from foraging on contaminated small mammals. Clearly, predatory and scavenging species are most prone to such toxic exposure and the almost exclusively documented response is death. (Appendix B). Even though it may take an animal several hours or days to die from anticoagulant rodenticides, most often a single foraging bout is sufficient to cause death. Therefore, the Agency is correct in basing the risk assessment on factors of acute toxicity. There is little evident that birds and nontarget mammals survive long periods of low-grade exposure to rodenticides; therefore, concerns about chronic and reproductive toxicity are substantially less than for pesticides applied in open fields and nature. In conclusion, this risk assessment is essentially an issue of acute risk and both the more subjective risk presumtions (Table 6) and the quantitative decision table (Table 7) adequately address the overall risk of rodenticide hazard to birds and nontarget mammals.

***Question 2. Are additional studies needed for better comparison of risks?***

No. At present, and for purposes of this risk assessment, sufficient data are available to develop a reasonable and defensible ranking of the nine rodenticides according to their potential hazard to birds and mammals. Additional information would be desirable on the primary toxicity to more relevant (i.e., likelihood of exposure) birds than northern bobwhite and mallard, but it is doubted that such experiments would affect the present risk assessment and I would recommend against such studies. As mentioned, little information is available on the chornic or reproductive hazard of rodenticides to wildlife. However, before such studies are seriusly considered, it must be properly established that there is an important likelihood of longterm, low-grade presence of first or second generation rodenticide in natural systems.

**Agency comment**: The Agency will require avian reproduction studies for all nine rodenticides. The RRTF and rodenticide registrants contend, and the Agency agrees, that the incident data (Appendix D in the final document) confirm exposure but not necessarily confirm mortality. The RRTF reports that a "threshold of toxicity" is needed to determine adverse effects. The Agency bases adverse effects on a no-observable-adverse-effects concentration (NOAEC) determined from avian reproduction studies with the northern bobwhite and mallard.

***Question 3. Is use of the "decision table" appropriate for comparing risks?***

Yes. The decision table is the main feature in this otherwise simplistic and rather obvious risk assessment. Whether each of the criterion used in the decision matrix are optimal could be argued. For example, I do not agree fully with the Agency's derivation of the dietary risk quotient or use of percent mortality pooled from a variety of highly disparet studies, but until other techniques are devised, the Agency's approach has a consistency that cannot be denied. With this consistency in mind, the Agency's decision matrix provided a graded distribution of the overall acute risk of the nine rodenticides under rieview for reregistration. Clearly, three of the rodenticides brodifacoum, difethialone and bromadiolone, graded much higher on a scale of 0-10 than any of the remaining six products.

As mentioned, the graded distribution of the nine rodenticides neatly separated the rodenticides into two groups, >6 and <4. Individually, these numbers are meaningless and I caution against using the decision table for a single pesticide. This is because toxicity, hazard and risk are all relative phenomemons. Exposure of an animal and death are definitive, but every variable used in the decision table is based on proportional responses; some live, some die. Another important aspect of the decison table is how each variable is weighted in importance. Weighting is highly subjective, but each is undoubtedly derived through the Agency's wisdom with much input from outside authorities.

Assuming the best available science and technical input provided the foundation for the decison table, it has provided the basis for important decisions regarding reregistration of selected rodenticides. However, should a product be approved or rejected because its summary rank is above or below an arbitrary number? Categorizing hazard or risk according to a numbering system has pitfalls because levels soon take on threshold importance (e.g., <5=safe, >5=toxic). What about that vague area between, say, 4 and 6? Instead, it is suggested that the arbitrary designators of "top", "second", "third" and "worst" used in the decision table (Table 7) be disregarded and that the results simply be considered with the continium of 0-10. Clearly, the rodenticides with high summary numbers pose greater risk than those with low numbers, but there may be extenuating factors of exposure that could affect risk. This, of course, is where the wisdom of the Agency reenters the decision process. Note: It is interesting that the choice of the terms top, second, third and worst implies the highest numbers are best (=safe) and the low numbers are worst (=toxic).

> **Agency comment:** The decision analysis has been revised, and the arbitrary designators of "top", "second", "third" and "worst" used in the decision table have been eliminated.

***Question 4. Is incident data useful in evaluating risks?***

Yes. Remarkably little field research is performed on pesticides in nature prior to their registration. Therefore, incident reports may be the only way a recurring problem can be

detected. These reports provide information on frequency of occurrence and insight into why the mortality happened. Only with this information can relevant laboratory studies be conducted to determine whether a causal relationship occurred leading to the incident. With this knowledge plus corroborating pathology (e.g., biochemistry, histological, residue detection), diagnostic techniques may be developed.

Unfortunately, incident reports underestimate the extent of mortality because there is usually a geographical imbalance in reporting of incidents and legitimate diagnostic effort and competency. For example, in New York and California, key personnel of the state wildife departments are strongly motivated to pursue and diagnose incidents of wildlife mortality (Attachment B). Fortunately, the Agency has implemented an incident reporting network that is invaluable.

***Miscellaneous:***

The Agency has not considered either the statistical error of data points (LD50, LC50) or the slope of the dose-response curve in the risk assessment. If they choose to continue development of decision tables and other more sophisticated statistical analyses, this oversight must be corrected. This is a grievous omission from a purely toxicologic perspective. (My feelings on this topic are well known to the Agency).

> **Agency comment:** The Agency has included 95% confidence intervals whenever available. Dose-response slopes are not available for most studies.

**SPECIFIC COMMENTS**

The following are specific technical issues that are supplemental to my response to your general questions. The focus is a critique of the data presented, with reference to the narrative presentation as appropriate. My overall impression is that the document was very well prepared, logical in presentation, and easily understood. Some data revisions and additions are recommended.

***Table 1. Comparative acute...dietary toxicity...***

This table is fundamental to the entire risk assessment, but is incomplete and misleading. Several changes are strongly recommended. Expansion of this critical table is warranted.

--LD and LC50s are estimators of toxicity that are presented in Table 1 as absolutes. The 95% CI should be added to provide evidence of the accuracy of the estimated LD and LC50s. If you choose not to include the 95% CI in Table 1, it must be added to tables in the supporting literature reviews. Likewise, slopes of the dose-response curves should also be added to supporting tables. The Agency requires these estimates for northern bobwhite, mallard and laboratory rat tests as part of the registration package; the data should be used.

--Example: The LD50 for the laboratory rats is 0.26-0.56 mg/kg for brodifacoum (Table 1). It is not clear what these numbers indicate. They are not supported by Table 8. Which number was used in development of the decision table? The basis for selection of all estimates (species, sex, age) must be described in the methods section and adhered to unless qualified otherwise. Erratic use of data will seriously taint the credibility of the decision table.

--The age and sex of quail, mallards and rats must be identified for each LD50 presented.

--Daphacinone: Were any toxic signs reported for the quail at 400 mg/kg? What percent mortality occurred at 2000 mg/kg? What level was used in the risk assessment? Were quail or mallard data used? Were any mortality or toxic signs noted at 5000 ppm in the quail study? How was >5000 ppm used in the risk assessment?

--Cholecalciferol: How could the LC50s be exactly 2000 and 4000 ppm for quail and ducks?

Tables and figures must stand alone in all scientific presentations. Table 1 does not. Also, the narrative does not explain exactly how these data were selected and used in the overall risk assessment.

> **Agency comment:** These comments have been addressed in the final assessment. Many of the data for these rodenticides were submitted and accepted when the Agency did not require determination of the dose-response slope and confidence intervals; thus, they are not available for many of the studies. Whenever available, the 95% confidence intervals have been included in the toxicity tables. The age and sex of test animals are not reported for most toxicity values obtained from the literature. Test requirements for Agency-required studies with the northern bobwhite and mallard have been included in the final document.

***Figure 1. Chemical structures***

This figure provides an excellent opportunity for a brief discussion of the comparative toxicology of similar chemicals, e.g., brodifacoum vs. difethialone and chlorophacinone vs. diphacinone. A brief statement of assumption is provided (p.2) regarding the similarity of brodifacoum and difethialone, i.e., differing only in substitution of a single sulfur atom for an oxygen. However, chlorophacinone differs from diphacinone through addition of a single chlorine atom, yet the toxicity of the two rodenticides is somewhat different, especially for dietary LC50s. Is this a question of stability? Please address?

> **Agency comment**: The similarity of brodifacoum and difethialone is based not only the chemical structures but also on the acute toxicity profile and physical/chemical properties, which differs little between the two compounds. An attachment displaying chemical structures and physical/chemical properties has been added to the final assessment (Attachment A).

***Table 2. Brodifacoum loading...***

This table is obviously idealized for demonstration and needs further discussion on p.2. The last two sentences of paragraph 3, p.2 are very important. It should be mentioned that when the rats had a choice there was no indication of aversion to the lethal bait. This concept is implied, but not stated.

Extremely important. How was "loading" determined? The implication is that rats simply kept eating and continued to become "more toxic." Without residue confirmation of increased body burden of brodifacoum, loading cannot be claimed. If a subject does not die promptly from a given exposure, metabolic processes will alter and permit excretion (or storage) of the chemical. Sometime residues plateau or even decrease over time even though the rate of ingestion and absorption may remain static. Either reconsider the concept of "residue loading" or provide analytical data to support the rate and degree of residue loading. The basic question follows: "Do rats on a constant diet increase their body burdens of biological active brodifacoum over several days of exposure?" Another way, "Are rats more toxic to predators over time of survival?" A table or figure should be constructed to illustrate such residue levels. This is a critically important aspect of this risk assessment.

**Agency comment**: The table has been removed from the final document.

***Table 4. Comparative risk...***

The table is a good concept. Several inconsistencies are of concern.

--Why are species mixed for LD50s? It would seem logical to use a single species or closely related species. Northern bobwhite data are used for 7 of 9 LD50s. I agree the northern bobwhite is probably the best choice because it would seem more likely to be exposed to most rodenticide applications. Yet the mallard with the lower LD50 (620 vs >2000 mg/kg) was chosen for warfarin. Was this because the 620 mg/kg result was from a better experiment (95% CI?) or because the 1-kg duck is the more representative species? Why is the >400 mg/kg LD50 used for disphacinone when Table 1 data suggests the true LD50 is near 2000 mg/kg? Why is the mallard 0.26 mg/kg LD50 used as substitute for 3.3 mg/kg reported for California quail dosed with brodifacoum? Certainly, the California quail is more closely related to the northern bobwhite than is the mallard. There seems to be a pattern of choosing the lower LD50. Is this appropriate? If so, the bias must be justified.

--An LD50 dosage (single exposure on empty stomach) is not equivalent to small doses from repeated exposure during foraging. Therefore, this table should be properly qualified, only be considered as guideline, and preferably restricted to a single species of similar size and physiological status. Furthermore, neither the 175-200 g quail nor the 1-1.2 kg duck is a proper representative (physiologically or toxicologically) of a 50 g bird even if the 50 g bird is a

juvenile bobwhite or mallard. These sources of variation (error?) should be addressed in the narrative.

> **Agency comment**: As indicated in the final document, the Agency requires only one LD50 test using either the northern bobwhite or the mallard as the test species. If LD50 values are available for both species, EFED policy is to use the value for the most sensitive species. Toxicity data are usually not available for smaller birds, which may be more sensitive than the bobwhite or mallard. Therefore, allometric scaling was used in the final document to determine food ingestion rates and the amount of bait providing an LD50 dose for birds weighing 25 g, 100 g, and 1000 g.

***Table 5. Comparative dietary risks.***

Excellent presentation. Solid, clear...

***Table 6. Primary and secondary risk presumptions...***

Good summary. Suggest "primary risk" column be added for mammals. It is realized that rodenticides are designed for primary toxicity to mammals and the results for most will be "high", but it needs to be stated. Part of the risk assessment is "nontarget" mammals.

> **Agency comment**: Primary risk to nontarget mammals has been included in the final document.

***Table 7. Decision table...***

Excellent presentation. However, "summary options" are bothersome. Is >7.5 clearly more hazardous than 6.25? Is >5 toxic and <5 nontoxic. Is the overall risk of brodifacoum and difethialone clearly greater than bromadiolone?

An alternative approach is suggested. Retain the color shade for ease of reference, but delete "option" terms. Simply consider the summary column as a continuum of 0-10. This relative ranking in conjunction with (but not exclusive of) supportive risk presumptions (Table b) will provide a sound basis for recommending or discouraging the use of different rodents, and of course for regulatory action. Finally, it is realized the point was to identify rodenticides of "greatest overall risk", but generally "top" is "best" rather than "worst" (=greatest overall risk) as implied herein. (Another reason to reconsider labeling!)

Finally, Attachment A details the development and use of the "decision table." It is intended as a tool to assist decision-making and reduce influence of "individual or group intuition" (=bias?). Perhaps this provides a quantitative validation of Table 6 (with which I agree), but how were relative weights determined (p.19, 102)? It is of concern that both primary and secondary risk to birds are of higher overall importance than for mammals. Is this an Agency bias? Please clarify.

**Agency comment:** The decision-analysis section has been revised and rewritten. The reported "weighings" were in error and have been corrected in the final document.

***Executive Summary***

Very well presented including solid summary table and conclusions.

***Introduction and Risk Overview***

Though pival is not being supported for reregistration, it should have been included in this prototypical risk assessment.

Risk conclusions are based on "weight of evidence". How are incident reports included in the risk assessment? They should carry some considerable "weight".

***Secondary risk to birds (p.2)***

The assumption that risks of difethialone are equal to brodifacoum is not necessarily correct. See above comments on Table 1 and Figure 1.

The concept of multiple LD50 doses is a simple reference point but bothersome and sometimes misleading. Also, basing all comparisons on LD or LD50s is of concern when not accompanied by the 95% CI and slope of the dose-response curve.

***Secondary-toxicity tests (p.6***)

Pooled percentage of mortality from a variety of tests is often misleading because the tests and treatment levels vary widely in design. Also, most often such tests do not relate to natural occurrences. For example, in nature, survival may be affected by natural stressors. Carefully reconsider how these data are used.

**Agency comment:** The Agency agrees that natural stressors can impact nontarget species to a degree not considered in laboratory tests in which the primary stressor is rodenticide exposure. Nevertheless, laboratory tests provide information on potential adverse effects, including mortality, bleeding, and delayed blood-coagulation time.

***Field studies and operational control (p.8)***

Comments were made indicating effects of prolonged bleeding of a wound. Is there evidence of infection?

It is evident that animals exposed to anticoagulants survive for several days. How might this affect a serious under-estimation of mortality, especially for highly mobile birds? And, will

birds foraging on rodenticide contaminated prey return to forage on additional contaminated prey? Have any telemetry studies been conducted to address this possibility?

> **Agency comment:** These are relevant questions and fruitful areas for research. Concerns about repeat exposure of predators and scavengers to contaminated prey have been raised in the final document.

***Incidents (p.9, Appendix B)***

Emphasis has been on circumstantial evidence, i.e., rodenticide residues in liver = death. Are any diagnostic criteria available that correlate residue level with response? Have whole body burdens of rodenticides been determined for victims of primary toxicity or for stomach samples of animals killed by secondary exposure?

> **Agency comment:** The significance of residues found in dead nontarget animals is unclear. The final document includes tabulations of available information on whole body burdens reported in target species.

***Risk Conclusions (p.17)***

Several times in the document "retention times in tissues of primary consumers" is mentioned. Does this mean prolonged residue burden in survivors? Please clarify.

> **Agency comment:** Data on retention time are obtained from metabolism studies in which rats or mice are given a sublethal dose and sacrificed at some later time.

# EXTERNAL PEER REVIEW OF

# Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals

BY

**Professor Raymond O'Connor**
**University of Maine**

## General Comments

This draft document comprises two components, a "weight of evidence" argument about the relative ranking of ecological risk from the nine rodenticides of interest and a decision support analysis based on the use of commercial software.

*The "weight of evidence" argument*

The bulk of the material in the document addresses the development of the weight of evidence argument. In general this part of the document is well -developed and it is hard to argue with the evident conclusion about each of the nine chemicals. These conclusions are largely implicit in the text since the task of deriving a formal assessment for each chemical is passed over to the decision support analysis. The case about each chemical is thoroughly and logically developed in this part of the document and the document is commendable in showing how the Agency staff have been able to develop the weight of evidence approach as a viable approach to the synthesis of a complex body of evidence.

A number of detailed reservations below involve specific points about the evidentiary presentation. Most of these involve minor clarification or suggestions to avoid bias, overt and otherwise. I see little difficulty in implementing these in a revision and see no need to dissent from the conclusions about the nine chemicals.

One major idea not discussed in the document and not raised below is that the "weight of evidence" argument might be supported by a meta-analysis (e.g. Hedges, L. V., and I. Olkin 1985 *Statistical Methods for Meta-analysis*, Academic Press, NY). Meta-analysis collates the results of a series of individual statistical analyses to ask how the overall pattern of results point to a conclusion. For example, a set of six separate analyses might each fail to yield statistically significant results, yet all (or most) point in the same direction, such that the entire set of studies

might be indicative of an underlying effect. In the present context each rodenticide yields a series of results ranging from data on toxicity through to behavioral information from field studies. In reviewing the text about field studies I was frequently struck by how consistent the data from the literature was about each rodenticide. It seems practical to consider compiling the results of the various studies as to mortality, bleeding, behavioral problems, etc., and to obtain overall significance estimates for the collated studies for each endpoint. In particular this could be an effective way of quantifying the evidence as to field incidents and returning a metric that could either be combined with other meta-analytical results or be transferred to incorporation in a decision support analysis. However, I do not see the need for this as critical.

*The Decision Support Approach*

In theory the decision support analysis advocated here provides an objective method of linking disparate data and eliminating subjectivity, a point well made in the text. Regrettably the deployment of the approach here is marred by errors and serious scientific short-comings and is not of acceptable quality to be released as part of a technical report.

What is particularly of concern is that this part of the present document appears to have been written without any regard for the comments of the SAP meeting of December 1998 on these issues. At that meeting (see the URL cited in the Attachment A) the Agency staff suggested an approach to comparative risk analysis very similar to that adopted here. The SAP endorsed many elements of the approach but emphasized in its Final Report the need to improve the approach on a number of fronts. In particular the Panel stressed the need for sensitivity analysis of any analysis attempted under this paradigm and also pointed out the problems associated with adding rank (ordinal) data from different metrics (See, for example, page 11 of SAP Report 99-1). It is true that the present document acknowledges the value of such analyses but they were not conducted and the results presented here. Apart from the issue of any variability (typically quite large) in input data, such analyses are needed to reveal to what extent the final outcomes are dependent on the weights attached to each criterion and metric, whether these are determined subjectively by the analyst or quantitatively by some computer algorithm. In my opinion the results of the decision support analysis presented here are essentially worthless without these analyses.

An additional problem with the present draft is that the discussion of the decision table analysis is extremely abbreviated. It certainly does not meet the criterion that enough detail be provided to allow another scientist repeat the work on the basis of the description presented. Some of the write-up appears to be formulaic, following closely accounts perhaps in a manual and editing it to match the circumstances of the present analysis. Whilst doing so may well provide a level of comfort to Agency scientists working with unfamiliar software, it does result in some weird outcomes, such as describing the most hazardous rodenticide as the best option and in adopting a color classification that encodes the most hazardous chemicals in green and the safest ones in red!! I have detailed below many of the specific points on which I found the write-up of the decision table work inadequate and will not repeat them here.

I cannot endorse the write-up of the decision table analysis as worthy of publication. It requires such a comprehensive re-write as to be essentially a new document requiring further

independent review. However, I doubt that the conclusions as to the two most hazardous compounds will change following such re-working. Unless there exists management concern about some of the lower ranked chemicals, the most cost-effective procedure may be to simply delete this part of the document in its entirety until the Agency staff gain more experience in the deployment and writing up of decision table analysis.

**Agency comment:** The decision analysis has been rewritten, expanded and the methods and approach have been clarified in the final document in response to Dr. O'Connor's comments as well as others. A sensitivity analysis also was performed.

**Detailed Comments**

**Agency comment:** Many of the comments below have already been addressed in the final document.

In the following, the notation PxLy-z indicates a reference to the text on Page x at or about Lines y-z.

P1L2 This title implies a comparative risk assessment which is probably approximated here if exposure is comparable across all nine chemicals. However, it seems intrinsically unlikely that this comparability will be the case. For example, zinc phosphide is targeted to the control of field rodents and this is likely to result in it having a very different exposure regime with respect to birds (the taxon at risk) than a rodenticide used largely within buildings. This point is well acknowledged within the text of the document but the implication for what the document then describes seems to have been overlooked. In many respects what the document addresses is what would formerly have been termed a comparative assessment of hazard to wildlife.

**Agency comment**: The assessment is a comparison of potential risks among alternative rodenticides. Comparisons of risk should be made among rodenticides that are likely to be used at similar, specific sites, not among different sites. Thus, risks of zinc phosphide used against ground squirrels in California should not be compared to the risks of bromethalin used to control rats in New York city. Risks can be compared among rodenticides when used at the same site, in which case exposure would be the same regardless of which rodenticide is used.

P1L20-22 It is worth noting here that the "weight of evidence" arguments here are well handled but the decision table approach is very poorly implemented. The latter is addressed further elsewhere in these comments.

P1L36 Note that this focus on field use inevitably mean that exposure is unlikely to be constant across chemicals, an assumption made in this document. This weakness does not negate the value of the overall analysis presented in the document but does require explicit addressing.

P7L5-6 The numbers cited here are confusing, it not being clear which refer to numbers of species and which to numbers of individuals. I would typically read a statement such as "... 5 test species, including 5 owls and 5 corvids." to mean five different species of owls were studied and five different species of crow were studied. I suspect that this is not what the author means here and the text should be modified accordingly.

P8L30 Spelling of "succumbed"!

P9L14 The high frequency of brodifacoum incidents noted here does at first sight appear convincing. However, the statement needs to be coupled with an explicit statement about its relative use: if brodifacoum were used on 1000 times more intensively (however measured) as diazinon, this sentence would not carry the same implications as if diazinon were the compound more commonly used.

P13L18-19 The frequency with which residues of multiple rodenticides were found in carcasses is a point notably lacking discussion in this document. The authors properly acknowledge these occurrences, but I don't think they do justice to the implications of the findings. Two issues relating to this point interest me. The first is why so many multiple residues occur (or is the apparent frequency of multiple exposures no more than one would expect from the use patterns of the nine rodenticides)? Is it the case that users are deploying an array of rodenticides in particular locations? If so, why, and is there room for regulatory action that might reduce the adverse effects of such multiple exposure? And if use of a chemical array is not behind the high frequency of multiple residues, what is? The second concern in have is that multiple residues confound the interpretation of the results. This may arise because when chemicals A and B are both implicated in a death, A or B may be the primary cause or both may be effective or there may be synergy between the two such that death results from exposure to the combination where exposure to either alone might not be hazardous. This problem would certainly have affected the decision support table had incidents been incorporated into the analysis (since a degree of correlation across rodenticides is introduced thereby). It is less clear as to the extent to which the phenomenon might be influencing the "weight of evidence" argument. I would recommend that the document authors should take a critical look at how these multiple residue cases are treated in reaching the conclusions presented.

**Agency comment**: The Agency agrees that the frequency of multiple residues (~10% for the anticoagulants) is an issue warranting further investigation.

P14L37-40 These four lines imply that label restrictions will alter the pattern of use of these chemicals. However, the *comparative* analysis of "risk" offered in the document does not allow for such differences i.e. the distinction between hazard and risk arises here also. Again, I am not terribly concerned about the semantics of risk versus hazard from the Framework document, merely that the distinction is substantive in places, as here.

P17L31 While this sentence is true, it is also a bit trite: one is almost certain to find some differences, so I would re-word this sentence towards greater substance. For example, a sentence along the lines of "... the Agency concludes that brodifacoum and difethialone are substantially more hazardous to wildlife than are the other seven rodenticides considered ..." would have more focus. In particular, I want to urge using a conclusion-laden sentence at this point in the text because a trite sentence otherwise seems to imply that the actual relative ranking of the compounds depends on the decision support table. As I explain elsewhere, I neither think this needs to be the case nor that it can be, given the poor implementation of the decision analysis here.

P19L1-4 I consider the explanation of procedure here to be too terse to be useful. I recognize that the attachment goes into more detail but more is needed here. In particular, greater emphasis is needed as to the "ratings" being rankings (they are?) and as to the subjective nature of the weight to be attached to each criterion. I also think more explanation as to why only the four categories considered here were used in the analysis, with explicit explanation as to why the incident data were not included in the decision table. It would also help to discuss explicitly the extent to which the "weight of evidence" argument might differ from the decision table one as a result of considering incident data (and associated use data, etc.) with the former.

P19L8 Here (and in the corresponding succeeding lines) some discussion of how terms `.

P19L23 Since there is only one criterion presented for primary risk to mammals, "criterion' rather than "criteria" is appropriate here.

P19L27-29 It is very undesirable to use "best" and "worst" in this way here. Doing so results in designating the most hazardous chemical as the best option, totally the opposite way to everyday use of language. I also recommend against using "option" in this context. Both pieces of terminology come from unthinking transfer of *DecideRight*'s table as to the best decision to the present analysis where values are actually the opposite way round.

**Agency comment**: The descriptors "best" and "worst" have been removed.

P19L36-37 This sentence is correct as it stands but could be read as implying that only these two chemicals should be so limited. I believe the true intention here is to recommend that these two rodenticides be *added* to the restricted use chemicals listed at the bottom of page 14. Re-word to minimize the risk of ambiguity. In addition, making it clear that the conclusion is to add brodifacoum and difethialone to the restricted use list emphasizes that these two chemicals share the attributes of the others that put those others on the restricted use list in the first place. This is an argument much easier to defend on the present data than any conclusion that brodifacoum and difethialone are absolutely more hazardous than the others

(which is actually probably true but does not need to be defended as the only rationale for re-classification).

P23L20-23 This text emphasizes the extent of variability in response of animals to exposure to the rodenticides, yet nowhere in the present draft is any consideration given explicitly to the uncertainty this introduces into the conclusions reached.

P23L32-33 I agree with this conclusion but note again that its significance depends on the usage of brodifacoum. The text needs to address the response that a massive market share inevitably results in a relatively small number of mishaps that are unimportant in context. (For example, finding birds killed by flying into glass windows is not an argument for abolishing windows). The point needed here is not a development of the arguments about the relative values of different rodenticides but rather about the reality of the claim for "... a high potential for secondary risk...".

**Agency comment**: Usage information for all nine rodenticides would be useful. When preparing the Reregistration Eligibility Document (RED, 1998), the Agency requested that registrants provide usage information, but none was provided.

P26L1 The species of harrier involved should be stated if known, otherwise the entry should indicate that this was unknown.

P30L25-26 This point is important only if there indeed exist areas where rats and mice are both important in the diet of barn owls and where brodifacoum is likely to be deployed to control them. The following paragraph (lines 30-36) testifies to the existence of such areas but leaves open the question whether they are common or not. Part of the arguments for the document's conclusions depends on such areas being fairly common, so the point should be discussed here.

P31L11 This point is made in several places in the text, and is compelling. It may need greater emphasis in the synthesis of conclusions.

P32L1-8 Given this finding for brodifacoum, it might be worth considering gathering up the evidence of non-lethal effects (or absence of evidence) across the nine rodenticides and using this as a separate topic in the final synthesis of the weight of evidence. If sub-lethal effects are largely known only for brodifacoum, the point is significant!

**Agency comment**: The issue of possible sublethal effects will be addressed through avian reproduction studies.

P34L38 Syntax problem!

P38L3-10 This evidence is very telling! I would be inclined to find some way to include it in the decision table analysis, for completeness.

P41L31-34 I agree!

P42L12-14 Note that whilst the retention time is long, these data also show elimination of a greater fraction of the chemical than is the case with brodifacoum. This point might deserve some explicit discussion here.

P44L12 It seems to me that this compound has less of an impact on birds than one might expect of the raw toxicity. This might deserve explicit discussion?

P45 In the column headed "No. survivors exhibiting symptoms" are some very useful data in support of the arguments about relative toxicity of the different compounds. To a degree the document doesn't fully exploit these data (as they appear in the corresponding tables for each rodenticide) for comparative analysis of the nine rodenticide hazards. It is arguable that these data should be incorporated into the decision analysis and into the meta-analysis suggested above.

**Agency comment**: The Agency agrees that these are very useful data and that mortality should not be the only endpoint of concern. However, some studies did not report whether adverse effects other than mortality were observed, and those that reported such effects did so in different manners that make them hard to compare. For example, animals were necropsied to observe for hemorrhage in some studies, whereas external bleeding and/or blood-coagulation time was reported in others. Thus, this information is not included in the decision analysis. Nevertheless, the information is considered in the "weight-of-evidence" approach.

P50L24-25 Again (for emphasis), this is an example of where many of the animals tested had multiple rodenticides represented in the residue analysis results. What is it about these that generated this result?

P53L21 "...was deemed comparable ..." is ambiguous. Who deemed it so - Grolleau (19690 or the authors of the present document?

P53L28 Missing year in citation!

P54L43 Is it "uncertain" or "never recorded"? Don't push the data to make an unsupported point: doing so detracts from more firmly founded conclusions!

P61L11-22 I find it interesting that there were so few cases with multiple rodenticides represented in the residues here. Why the contrast with other chemicals?

P67L14-15 True, but the argument also requires that this selective feeding be to an extent that the volume x rodenticide density product be large relative to other dietary items. Is this likely, or is the text pushing to favor a conclusion of risk?

P71L34-35 Elsewhere in the document, if a chemical was thought toxic and some deaths were found, it was accepted that this was good enough support for a conclusion of toxic

effects, without explicit consideration of possible confounding effects. To some extent the text at this point seems to be trying to argue that the chemical really is toxic but that there were reasons other than non-toxicity as to why the magpies did not subsequently die. This smacks of double standards! It might be worth looking carefully through the document to make sure there is no unconscious bias towards "convicting' a chemical come what may!

P73L32-33 See P71L34-35.

P82L14 Two minor grammatical points: 1) I would not use "mortality to birds" but "mortality of birds", and 2) although the mis-use is common, mortality is a class noun, with "mortalities" being inappropriate (use "deaths" where a plural is needed, and mortality as the opposite of survivorship). These errors appear throughout the manuscript.

P85L32-37 Examples of where the assumption of equal exposure across chemicals doesn't hold!

P86L9-12 And again!

P87 The data in this table cry out for inclusion in the decision table analysis! These are he kind of data that adjust the analyses for real world exposures.

**Agency comment**: The remainder of the comments refer to the decision analysis and its presentation in the appendix. The decision analysis has been revised in the final document to address the comments below. The SAP made many helpful suggestions in 1998 to improve the utility of the methodology presented for use in comparative analyses of ecological risk from pesticides. There are, however, two recommendations that the panel thought critical for valid results: risk quotients - risk indices which are used to express risk from pesticides to nontarget organisms, should never be combined (added); and, a sensitivity analysis should always be included. Following this advice, no risk quotients or indices have been added together for this analysis, and a sensitivity analysis has been included.

P104L14 The document notes that the Agency "presented" the comparative analysis approach to the SAP, which could be red as implying that the approach was approved by the SAP at that meeting. The reality is that the SAP (as documented in the URL cited in footnote 2 in line 17) entered extensive reservations about the way the Agency proposed going about the analysis. In particular, the SAP offered several recommendations as to how this type of analysis should be conducted to be of high standard. Regrettably, several of these recommendations are ignored in the present document! I emphasize that the fact of having "presented" the approach to the SAP does not warrant any implied claim that the version used here is scientifically sound. It isn't!

P104L24 " about 29-years ago ...": why the "about"? Since delays in approval etc., of the present document are inevitable, surely "about 30 years ago" would be adequately precise.

P104L31-32 They can indeed be dealt with by sensitivity analysis. So why wasn't this done here, particularly in the light of the strong recommendation to this effect offered by the 1998 SAP? I want to emphasize that a decision support analysis is essentially meaningless in the absence of sensitivity analysis. One has to show that the conclusions reached are robust against variation in the input data and in the weights chosen by the analyst; otherwise the data are effectively noise or the conclusions are the inevitable outcomes of the subjective decisions of the analyst.

P104L32-33 I think it is dangerous to ignore these interactions and correlations. One can detect the effects of correlated input data by simply assigning zero weight to each variable in turn and doubling the weights assigned to its potential correlate: a correlated variable has no effect on the overall scores when this is done!

P105L14 Here and elsewhere throughout the attachment, the plural form "criteria' is used where the singular form "criterion" is needed. (The main body of the text gets this right.)

P105L9 I do not recommend the use of "options" in this context. I suspect the term is used in the *DecideRight* manual which focuses on choosing among options for action, but here the choice is among chemicals and not among options. Using appropriate terminology will avoid generating wrong impressions and in particular will avoid the confusing conclusion that the "best option" is the chemical with the greatest risk associated with it!!!

P105L19-20 Why the "As ...., ...are assigned"? The process of assigning weights to each criterion is totally independent of the selection and does *not* depend on the selection of "alternative options" (here the ranking of rodenticides). The analyst is free to assign whatever weight he or she chooses to each of the criteria considered, needing only to be able to justify it to his or her audience!

P105L23 Again "under each criterion"!

P105L26-29 This choice of color scale leads to the silly result that the most hazardous rodenticide appears in green and the safest in red!!!! This is completely counter-intuitive.

**Agency comment**: The color scale has been eliminated in the final document and the terms "criteria", "criterion", "choice(s)", and "factor(s)" have been eliminated.

P105L32 Based on what the authors here tell me, and on what I already know about decision support tables, I understand the process involved to be no more than a simple weighting of each criterion and calculation of a weighted sum of ranks (possibly

with each scaled to {0,1}) across criteria within chemicals. If this is all that is done, then describing this as "underlying mathematical algorithms" is unnecessarily pretentious. If, on the other hand, my understanding of what is being done here is wrong, then substantially more detail as to the computational steps is needed to avoid any hint of the whole thing being a "black box".

P105L41 "... other scales can be input for the ratings for each criteri**on**". I don't understand what is intended by this. Clarify!

P106L26 Since only LD50 data are used here for mammals, yielding one criterion, but both LD50 and LC50 data are used for birds (yielding two criteria), there is a differential in the treatment of birds and mammals. This can introduce bias. (To see this, assume that there is just one metric for each criterion. Then the mammal criterion is certain to put one chemical into rank 1 and another into rank 9. For birds however, getting *both* criteria into rank 1 is needed to average to rank 1 (assuming equally weights for the two criteria): should one criterion be 1 and the other 2, the average score becomes 1.5; with one being 1 and the other 3 the average score is 2.0 and so on. Hence having only one criterion pre-disposes that taxon towards having more extreme values. Of course the likelihood and magnitudes of these potential biases change with unequal weights across criteria and with the number of metrics within each. However, absent sensitivity analyses the present results are not assured to be unbiased.

P106L34 This "migration" is irrelevant to the analyses, merely being a convenient device towards effective visual portrayal of the results. The same numbers will emerge without this migration, so the emphasis on the migration of rows and columns (repeated several times in the document) is uncalled for. It can potentially lead naive readers in the wrong direction.

P106L35-37 See P105L19-20

P106L36-37 "weights are assigned ... so that they are ranked in order of their importance in fulfilling the overall task". First, this language seems to have come straight from the *DecideRight* manual's description of reaching a management decision. It needs to be re-worded to reflect the present goal. More importantly, as written there is significant ambiguity in the description because of the proliferation of "they" and "them": the "they" in "... so that they are ranked ..." is likely to be read as meaning "options" (here rodenticides) whereas what is actually intended is that it mean "criteria". The text needs to be re-worded to address this problem.

**Agency comment**: In the revised document, all calculations were performed using *Lotus SmartSuite 1-2-3*®. The *DecideRight*® software was only used to check the calculations.

P106L40-43 This section contains inadequate information from which to work out what was done. The detail provided does not allow one to follow through the steps oneself. (I will be more specific below).

P108 From the text provided to this point, one cannot tell how the value of 63.00 (or 0.26 etc.) was obtained. Nor is it clear how one might obtain a summary value of 10.00 from the values 63.00 and 0.26 (and so on for other rows). The text outside the table box refers to the weight for each criterion as being "High" but as this is not quantitative one cannot do the computations from the information provided. Additionally I found the final sentence (below the box) to be rather terse: I can guess what is intended but it could be clearer.
In the following diagrams (P. 109-) the same questions come up.

P111 Logically there should be a table, albeit with just one criterion, for the Primary Risk to Mammals. Presumably because this was not included explicitly the numbers for this column on p.112 run the wrong way (from low to high)???

P112L4-5 This explanation of the diagram on page 113 is totally inadequate.

P113 I cannot make any sense of this diagram. The legend on page 112 speaks of the relative *strengths* of the various *choices* in each of the *factors* but the text doesn't provide any guidance as to what the three italicized words actually refer to. I thought they might mean the coefficients (or a scaled version thereof) shown for the four "Risk" columns on p.112, but this cannot be. For example, for warfarin the three colors on p.113 do seem to be in the proportions of the corresponding numbers on p.112 but the white bar is totally out of proportion (or is this a consequence of the error raised about P111 above?). Similarly the data for bromethalin and the data for zinc phosphide do not match with the corresponding color bars on p.113.

P113 Let's assume that the diagram on p.113 is indeed supposed to display the proportional contribution of the coefficients on p.112 to the overall score. Then the colored bars actually tell us nothing beyond what we can already get by examining p. 112. The only advantage would be if we used a fixed baseline (as for the red bars on p.113) to show immediately the relative contributions of that criterion for each of the nine rodenticides. This will not be achieved by the cumulative bar chart of p.113: it needs to consist either of four histograms (bar charts) aligned by rodenticide so that one can scan across and see which rodenticides has big or small components therefrom, or it could consist of nine blocks of four bar charts i.e. 36 bars from left to right - on a common baseline, allowing one either to scan across a given color (variation in that criterion across rodenticides) or within rodenticide (relative contribution of the various criteria for that rodenticide).

P114 At this point I would expect some presentation of sensitivity analyses. Such analyses identify which criteria (or metrics) are particularly big sources of uncertainty and how much uncertainty in the final assessment is derived from each criterion (and beyond that, metric). One obvious source of information as to the levels of uncertainty to evaluate is the variation in toxicity values across the species measured, and analogous information for the other metrics. Where the

variation for a chemical is inadequate, the sensitivity should be evaluated using a percentage change figure based on typical data for other chemicals. Alternatively, sensitivity could be assessed by simple application of a 10% (or some other percentage reflecting real data) change to the metric for all the chemicals. This would then yield a standardized set of data on how the overall scores would have changed for a 10% change in each of the individual metrics contribution to the overall score. Similarly, the final outcome depends on the weights to be attached to each criterion (and each metric within criterion) and these are rather arbitrarily defined. They may well prove to be appropriately chosen but one needs to be sure that minor differences in the choice of weights would not reverse one's conclusions, and sensitivity analysis is the appropriate method for determining the extent of this robustness or otherwise. Without some such investigation of how the decision support analysis varies as to outcome as inputs vary, the analysis presented here is but one instantiation of possible outcomes. Given the variation typically found among these chemicals, there are no a priori reasons to believe that the result obtained here is necessarily the most reliable result

**Agency comment:** A sensitivity analysis was added to the final document.

# EXTERNAL PEER REVIEW OF

# Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals

**BY**

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**ABSTRACT**

This EPA report contains a very comprehensive toxicology review of a literature database on the comparative risks of nine rodenticides to birds and non-target mammals compiled by the US EPA. The rodenticides evaluated include brodifacoum, difethialone, bromadiolone, diphacinone, chlorophacinone, warfarin, bromethalin, cholecalciferol, and zinc phosphide. For each rodenticide the available acute toxicity data for birds and mammals, secondary effects are well reported from laboratory studies, and information on mortality and exposure from field studies are provided. Secondary poisoning studies are particularly well and comprehensively reported. Information on residues in target species and retention time (toxicokinetic data) are also provided. Risk factors are compared in a rational and useful manner. Additional toxicokinetic information and a section on comparative toxicokinetics (or comparative metabolism and retention times) is recommended to improve the clarity of the report. Some additional publications relevant to the review and the risk assessments are identified and copies are attached to this report. I (Dr C.T. Eason) have over 10 years extensive research and practical experience in vertebrate pesticide toxicology and have published over 100 papers relating to the efficacy, safety, and comparative risks of vertebrate pesticides. On the basis of this experience, and the evidence presented in the report, I concur with the risk ranking. However, the ranking of diphacinone and chlorophacinone as having a high risk of causing secondary poisoning in mammals whilst having only moderate to low risk in birds, requires some written explanation in the summary section (as it is not clear why this is the case until much later in the document). Furthermore, it is noteworthy that a recent publication on difethalone (Goldade et al. 2000) presents findings which appear to conflict with the conclusions of this report regarding secondary risk. The risk of secondary poisoning of mammals is reported to be less than for birds. It conflicts with the weight of evidence for second-generation anticoagulants as a whole, which is clearly demonstrated by this report, and hence it is important that the Goldade paper is reviewed.

Some caveats need to be applied to the low risks for first-generation anticoagulants and the non-anticoagulants. New data covering cholecalciferol is suggested for inclusion which addresses both primary and secondary poisoning risks. This provides further evidence to underpin the

conclusions of the EPA document, but emphasizes that low risk does not mean no risk to non-target species.

There is a paucity of residue data from field studies in target species presented in the report on which secondary poisoning risk in the field could be cross referenced with the SMART analyses based on laboratory studies. It would be appropriate to recommend that improved databases on residues in target species would improve assessment of secondary poisoning risk (including RQ calculations). It is noteworthy that most if not all of the primary and secondary risk assessment studies reported take limited account of the implications of the comparative toxicokinetics. In field settings multiple exposure to a first-generation anticoagulant (separated by weeks or months) may not necessarily lead to increased risk. In contrast, bioaccumulation and enhanced toxicity would occur with the more persistent compounds. The limitations of existing study designs or RQs based on single exposures could be highlighted.

Finally it is worth noting (particularly as zinc phosphide, bromethalin, and cholecalciferol fair well in this assessment) that many veterinary toxicologists do not favour the non-anticoagulants. They all lack effective antidotes. Bromethalin is perceived by many to be unpleasant and inhumane (I have little personal experience of bromethalin, so I cannot amplify on these comments).

***N.B.*** Studies currently underway in NZ relevant to this review:

- Toxicokinetic comparison of warfarin, coumatetralyl, diphacinone, and brodifacoum — pilot complete — further work proposed 2001.
- Residue data in target species under simulated field studies (in pen and cage trials pending)
- Collection of residue in target (and non-target species)
- Proposed — comparative secondary poisoning after multiple dosing of first- and second-generation anticoagulants -— comparative risks
- Proposed — sub-lethal effects/anticoagulants.

## INTRODUCTION

This brief report is a toxicology review of a draft US EPA document entitled "Comparative risks of nine rodenticides to birds and nontarget mammals", and has been prepared by Dr C. T. Eason, Senior Toxicologist at CENTOX–:Landcare Research New Zealand Ltd for Tetrahedron, Inc. I (Dr Eason) have extensive experience of rodenticide toxicology and have published over 100 papers on fundamental and applied aspects of rodenticides including both anticoagulant and non-anticoagulant compounds.

## OBJECTIVES

The purpose of this toxicology review is to provide an evaluation of the report prepared by the U.S. Environmental Protection Agency. At the request of Tetrahedron Inc. the report provides:

(1) Written general comments and specific proposed changes or revisions required to improve clarity and scientific accuracy of the document.

(2) Any new data that might contribute significantly to change the document which was not considered by EPA should be included, or at least referenced.

It also focuses on the following criteria (provided by Bill Erickson 10 Jan. 2001)

- Is the assessment scientifically sound?
- Do the data support the risk conclusions?
- Do brodifacoum and difethialone stand out as posing greater risks than the other rodenticides?
- Is any relevant data missing that would improve the assessment?
- Are there any better ways of comparing risks?
- How should the incident data be used in risk assessment?
- Is the Decision Table analysis appropriate or of any use?

**TOXICOLOGY REVIEW**

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**<u>Part 1</u> "Written general comments and specific proposed changes or revisions required to improve clarity and scientific accuracy of the document"**

**<u>Part 2</u> "Any new data that might contribute significantly to change the document which was not considered by the EPA should be included or at least referenced"**

**<u>Part 3</u> Comments on the hazard identification and conclusions provided by the toxicity data summaries.**

**<u>Part 4</u> "Comments on dose response, end-points, and uncertainties"**

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(1) Executive summary, paragraph 2: states that the persistence characteristics for brodifacoum are essentially the same as difethialone. It is noteworthy that there is limited data on difethialone when compared to brodifacoum, in this regard. What there is suggests a shorter t ½ for difethialone of 108 days versus 180 days for brodifacoum in rat liver. I agree with the author that those "are similar" (given different experimental conditions etc.). However, to say they are "essentially the same" could be misunderstood.

(2) Executive summary, paragraph 2, final sentence: "The non-anticoagulant rodenticides are not retained in significant amounts in tissue of primary consumers" is not strictly accurate. I agree with the conclusion that they present "less secondary risk than do the anticoagulants". However, cholecalciferol metabolites can be detected some time after dosing and the "actives" are present at sufficiently high levels to induce secondary toxicosis in some situations (Eason et al. 1996a,b; Eason et al. 2000). Zinc phosphide will also be present in the gut and intestine. This caveat does not significantly alter the conclusions in the EPA document in regard to non-anticoagulants, but some adjustments to the text would be appropriate.

**Agency comment:** Data on persistence of cholecalciferol are included in the final document.

(3) Executive summary, paragraphs 3 and 4: The final sentence "Persons not trained or experienced in rodent control may be more likely to intentionally or inadvertently misuse rodenticides" appears out of place. It would be more logical (in paragraphs 2, 3, and 4) to deal with primary poisoning issues first then secondary poisoning, then related issues such as training etc. Sub-headings might help. Regardless of these minor changes I am in full agreement with the conclusion regarding relative risk.

(4) Executive summary (paragraph on mammals): This could be improved (as above) by dealing with primary toxicity first, then secondary toxicity. Comments regarding metabolism would be better placed between primary and secondary poisoning. The order currently is: secondary toxicity, persistence, anticoagulants, then non-anticoagulants, then primary toxicity.

[It will be difficult for readers to understand at this stage of the document why all the anticoagulants (except warfarin) pose a high risk to mammalian predators and scavengers, but some of these compounds are classified as low or moderate risk to raptors or scavenging birds, so clarification of how these conclusions are reached would be useful in this section. This is particularly important in view of the recent paper by Goldade et al. 2000 which provides information that contradicts this finding.]

(5) Table of contents: Note that under each compound, e.g. Brodifacoum, the order in which information is presented is Primary toxicity then Secondary effects. Recommend this order is the same in the Introduction and Risk Overview, as well as Executive Summary.

**Agency comment:** Many of the suggestions above have been incorporated into the final document.

**INTRODUCTION AND RISK OVERVIEW**

(1) Page 1, paragraph 1: At the end of the first paragraph it is noted that for some rodenticides there are few data available on toxicity. It would be worth mentioning here that the quality and quantity of data available on metabolism and retention times in rodents and non-target species are also variable. However, it is sufficient to identify the most persistent compounds. This is important because of growing international concerns regarding Persistent Toxic Substances (PTS). The ability to distinguish between those anticoagulant compounds which are uniquely persistent and those that have acceptable (shorter) retention times is a key issue. But unfortunately the quality of toxicokinetic data varies very considerably, and is particularly sparse for some first-generation compounds.

(2) Page 2, paragraph 1, final sentence: The statement here regarding non-anticoagulants is appropriate, even in the light of the new information provided on cholecalciferol (Eason et al. 1996a,b; Eason et al. 2000), i.e. cholecalciferol metabolites are retained for some

weeks in sub-lethally poisoned animals and are likely to be present in carcasses at significant levels, but less likely to be present at toxicologically significant levels.

(3) Page 2, paragraph 2: Caution regarding calling brodifacoum and difethialone half-life "nearly identical". "Similar" should suffice. It is noteworthy that the toxicokinetic data in difethialone is particularly sparse. The review paper that reports a t ½ in liver of 108 provides no raw data to substantiate this figure.

(4) Page 2, paragraph 2: Caution re storage of toxicologically significant amounts. the statement "much less likely than anticoagulants" (see para 1 page 2) would be more accurate than "not stored" (see final sentence para 2).

(5) Page 2, paragraph 3: Suggests change the work "claim" to "indicate". "Claim" sounds as though the author has a preconceived bias against company label claims.

(6) Page 5. Structure required for cholecalciferol.

(7) Page 7, paragraph 3: The Joermann (1998) reference is an important one. It might therefore be worthwhile expanding on the basis for Joermann's conclusions that brodifacoum is more hazardous than bromadiolone. Both are extremely persistent. The t ½ for bromadiolone in rat liver is 170 days versus 130 days for brodifacoum (Parmar et al. 1987).

(8) Page 11 and 12, final sentence page 11: There are numerous comments similar to "because they are more toxic and retained longer in biological tissues", through the document. It is also suggested that chlorophacinone and diphacinone are somewhat less persistent. I strongly believe a separate section or paragraph on comparing toxicokinetic parameters is needed, i.e. the comparative absorption, metabolism and persistence of brodifacoum compared with other anticoagulants is important.

Please see Appendix 1 for a suggested script and summary table (this includes all available publications that I could source — the EPA author may wish to delete extra compounds, e.g. flocoumafen). However, note to some, flocoumafen references might be useful as the toxicokinetics of flocoumafen have been particularly well studied. The script and table is provided as an example of a possible style. The author can adapt this to his needs. However, please note that this text is similar to the text to be published by Eason et al. 2000: Risk Assessment of Broadscale Toxicant Applications for Rodent Eradication on Island versus Mainland Use in Pest Management 11. This paper is attached (in proof form) will be forwarded to Bill Erickson to reference. Please cite this reference if using or adapting the material in Appendix 1. A similar approach, providing a review of the metabolism for non-anticoagulants would also be appropriate (see Eason et al. 1996b).

**Agency comment:** A section on toxicokinetics has been added to the final document.

(9) Page 12, paragraph 2: This section indicate that the risk to mammals from secondary poisoning from diphacinone or chlorophacinone (and second-generation anticoagulants) is

greater than the risk for birds. Some explanation for this would be appropriate here or in a concluding section. This might be because the indandiones are more toxic to other mammals than to birds? Are the $LD_{50}$ values for anticoagulants lower in mammals than birds, or is it simply that birds will eat less. Some explanation or synthesis by the author would be appropriate to clarify this.

(10) Page 12, paragraph 3: As indicated earlier I have attached a copy of the paper Eason et al. 2000: Non-target and secondary poisoning risks associated with cholecalciferol. This concludes that "the most distinguishing feature of cholecalciferol is a lower risk of secondary poisoning when compared with 1080 and brodifacoum", which concurs with the EPA report. However, our secondary poisoning studies in dogs indicates that there is a risk of hypercalcaemia and adverse effects on target organs, such as the kidney, in dogs repeatedly eating carcasses of animals poisoned with cholecalciferol baits. This risk would be extrapolated to other mammals. It is noteworthy in this regard that very few secondary toxicity studies (e.g. Marshall 1984) include data on body weights, blood chemistry and pathology, which is a significant oversight for both non-anticoagulants and anticoagulants.

(11) Page 12: In the field studies section you may want to include additional/update UK data from Shore et al. 1999: Exposure of non-target vertebrates to second-generation rodenticides in Britain, with particular reference to the polecat, *Mustela putorius*. *NZ J. Ecology 23(2)*: 199–206. In the package I am forwarding by post to Bill Erickson, I am including Vol.23 of the New Zealand J. Ecology.

(12) Page 13, final paragraph: Please note that in the paper by Eason et al. 2000 we confirmed the low toxicity of cholecalciferol to birds. Confirming the duck data, however, significant mortality occurred in canaries and chickens. It might be wise to say cholecalciferol is "less toxic to birds" rather than only slightly toxic. N.B. Table 4 states cholecalciferol is "practically non-toxic to birds". Should be toned down or altered "practically non-toxic to mallard ducks" or "has low toxicity to mallard ducks", or "appears to have lower toxicity to birds".

**Agency comment:** This change has been made in the final document.

(13) Page 14, paragraph 3: This section is focused on primary risk to birds, hence the Palmer (1999) reference relating to deer appears to be out of place and should go in the next section of p.17.

(14) Page 15 and 16: The comparative risk assessment on Table 4 and 5 are excellent and should be extended to cover some non-target mammalian species in terms of primary poisoning. Additional dimensions could be added:

(i) the amount of bait likely to be eaten in a single feed. While the RQ and agency standard on Table 5 are satisfactory and accepted, the values could be more meaningful if they were related to the amount of bait/toxin likely to be ingested in a single feed versus the amount needed to kill a bird.

With regard to the RQ derived on Table 5 or the alternative methods of calculating RQ, it must be emphasized that these values are based on single dose and the risk from multiple exposures will be greater for the persistent second-generation anticoagulant rodenticides (SGARs) because of their tendency to bioaccumulate versus first-generation anticoagulant rodenticides (FGARs).

(ii) With regard to secondary poisoning risk to non-target species, similar calculations could be based on typical residue profiles found in non-target species, the susceptibility of non-target species, and the amount of tissue likely to be eaten in single and multiple feeds (see Goldade et al. 2000).

(1) Pages 17, 18, 19: I agree with most of the risk assessment summary, but note that the retention time for bromadiolone in liver is greater to that of brodifacoum, hence the risk of bioaccumulation for bromadiolone is considerable. It is noteworthy in this regard that the difference between difethialone and bromadiolone on Table 7 in terms of the summary values for overall risk is small (7.52 and 6.25, respectively), whereas there is a substantial difference between bromadiolone and diphacinone (despite the paucity of toxicokinetic data on diphacinone).

(2) Page, 17, sentence 2, paragraph 1: under Risk Conclusions states that "Risk to mammals are less pronounced". This contradicts the summary table and underpins the need for clearer elucidation of the comparative primary and secondary risks to mammals as well as toxicokinetics in this overview section.

**Agency comment:** This statement has been reworded. The Agency meant to state that the comparative risks to mammals differed less among the rodenticides than do the comparative risks to birds.

The methodology behind SMART is not clearly presented (for those not familiar with it), e.g. what is meant by the term "options" on p.19? I found the explanation for the risk ranking process in the appendix confusing. It could be more clearly and concisely presented in this section.

**Agency comment:** This section has been revised in the final document.

If bromadiolone is still to be allowed as an OTC or other first-generation compound (with no or limited toxicokinetic data) perhaps label instructions should be changed or tightened up alongside any proposed tightening up on the use of SGARs.

It is important that non-anticoagulants, particularly bromethalin and cholecalciferol, are not viewed as "safe" as a result of the risk ranking in this report. Both can cause toxicosis in non-target species, and poisoning of pets with these compounds or zinc phosphide has been a concern to veterinary toxicologists worldwide.

**Agency comment:** The comments below refer to the individual chapters for each chemical included in a previous draft. The final document was revised and the information from these chapters incorporated into other sections of the assessment.

**BRODIFACOUM SECTION**

(1) Page 21, under Primary Toxicity: Some general introductory statement after the first sentence would be appropriate, e.g. In a number of birds the $LD_{50}$ values are 1 mg/kg or less and birds are highly susceptible to brodifacoum.

(2) Pages 24–28: It is worth noting that no secondary poisoning studies have been conducted where exposures have been repeated in survivors, i.e. all studies provide birds or mammals with rodents for a few days on one occasion. In the field 2nd or 3rd exposures could occur months/years after the initial exposure and lead to bioaccumulation, even when the intervals between exposure were months or years. This is an important implication of the hepatic t ½ > 100 days and is not addressed by any of the cited publications. If repeat exposures were to occur with warfarin several months after the initial exposure, then most if not all the hepatic residues would have been voided and the risk of bioaccumulation would be low. A statement addressing the issue of multiple exposure would be worth including in the overview section (if not in this section).

**Agency comment:** This has been noted in the final document.

(3) Pages 29–36: There is extensive reporting of field studies and operational control in the report. Some of the data is arguably irrelevant to current use patterns for commensal rodent control in the US. The rationale for inclusion of this data needs to be made/reiterated on p.29 under the heading Field studies and operational control. Alternatively, those studies that are more relevant to US current use patterns need to be highlighted and more weight needs to be attributed to them than, for example, the New Zealand studies.

**Agency comment:** Information from field studies and operational control programs is provided in the rodenticide assessment, because they indicate that exposure can have adverse effects on nontarget organisms. Unfortunately, few studies have been conducted for rodenticide use "in and around buildings", which is the predominant use of most of the rodenticides in the U. S. Therefore, the Agency has had to rely more on laboratory and field studies to assess potential nontarget risks.

In relation to our experience with brodifacoum in New Zealand, I have enclosed the most recent publication, items “in press” and submitted, for your reference.

(4) Page 33, final paragraph: There are very mixed feelings about the proposed use of brodifacoum for secondary poisoning and it has been discouraged; not just because of the indiscriminate contamination of food chains, but because some predators seem to tolerate quite high concentrations of brodifacoum in the liver. This apparent survival of predators with quite high concentrations of brodifacoum (see papers posted to Bill Erickson) doesn’t

tally well with pen trials for various compounds, and summary conclusions in the EPA report indicating that non-target mammals are at greater risk than non-target birds.

**Agency comment:** The Agency believes that nontarget birds are at risk from some of the rodenticides, including brodifacoum.

(5) Page 34, final paragraph: Note there is a Shore (1999) paper as indicated earlier (see NZ J. Ecol. 23(2) enclosed).

(6) Page 36, Residue data: Please see the book chapter by G. Brown in the Rodenticide book by Alan Buckle. There are data in rats presented in histogram form. This sort of data is extremely important for calculating secondary poisoning risks from eating carcasses. (copy included in package to Bill Erickson).

**Agency comment:** Available residue data in target species have been tabulated in the final document.

(7) Brodifacoum – Retention in animal tissue: See appendix and attached paper. I am not familiar with the Brett and Hudson (1979) unpublished paper, but have attached all other material I could get my hands on – please see Appendix 1.

In relation to paragraph 1, I am surprised by this information. It is my belief from reading the toxicokinetic papers on flocoumafen that substantial amounts of a dose of brodifacoum would be excreted in faeces (some not absorbed and some re-entering the gut via the bile). If a very low dose was given then most of the dose might be retained, but if high doses are given or repeated doses then the proportion excreted in the faeces increases. In this regard it is important to provide the dose of brodifacoum given (see Huckle et al. 1989 and Huckle and Warburton 1989, cited in the papers forwarded — these two papers relate to flocoumafen, which can be considered to be very similar to brodifacoum). Note that on p.42 you report 47% faecal elimination for difethialone. I wonder if the brodifacoum dose was proportionately less than that in the difethialone study? Please check.

**Agency comment:** Additional information has been included in a toxicokinetic section in the final document.

**DIFETHIALONE SECTION**

(8) Page 41, Regarding the difethialone secondary poisoning statement that "the Agency is not aware of any studies conducted to assess possible secondary risks to birds and mammals exposed to difethialone-poisoned rodents." However, there is a recent publication (Goldade et al. 2000: Design of laboratory secondary hazard study. *In:* John J. Johnston (*ed.*) ACS Symposium Series 771: 146–156). This paper uses difethialone as a case study and reports risk quotas for secondary poisoning of ferrets of <0.001, and for magpies of 0.036. In this paper $LD_{50}$ for difethialone in ferrets is presented on p.153 at 760 mg/kg. This figure is most unusual for a second-generation anticoagulant, and is inconsistent with $LD_{50}$ presented for other species (see Table 13).

The significance, validity, and consequences of this paper need to be explored in the comparative EPA risk assessment review of rodenticides, since the findings of this paper conflict with the findings of this review on a number of counts (i) low risk of secondary poisoning with difethialone, (ii) less risk of secondary poisoning in mammals than birds.

**Agency comment:** The Goldade study toxicity values are cited in the final document. However, more information on some details of the study, including aspects of the methodology and the mortality at the different doses tested, are needed. The information was requested from the study authors, but they deferred the Agency to the study sponsor. The sponsor said the study will be submitted to the Agency, but has not yet done so. Therefore, the Agency does not have the relevant information to further evaluate the study.

**BROMADIOLONE SECTION**

(9) Page 48, Retention in animal tissue: Add "the persistence of bromadiolone is similar to that of brodifacoum. The half-life in the liver of rats is reported to 170 days (Parmar et al. 1987) and residues have been detected in sheep liver for 250 days (Nelson and Hickling 1994) (see Appendix 1).

**CHLOROPHACINE SECTION**

(10) Page 53, For secondary poisoning see Primus et al (2000): Chlorophacine Residues in Rangeland Rodents : An assessment of the potential risks of secondary toxicity to scavengers. *In:* John J. Johnston (*ed.*) ACS Symposium Series 771: 164–180.

(11) Page 57, final paragraph: When discussing retention and bioaccumulation it is important that consideration is given to the dosing interval. Aspirin is a rapidly eliminating drug, but if an individual takes aspirin every 2 hours bioaccumulation will occur. The sub-chronic studies represent daily administration for 28 days. Bioaccumulation of any anticoagulant, even warfarin (dependent on dose) would be likely in these circumstances (i.e. repeated dosing every day) and more probable with SGARs.

**Agency comment:** The residue data provided in Primus et al (2000) are included in the final document.

**DIPHACINONE SECTION**

(12) Page 65: There is a retention study available in cattle? See Bullard et al. 1976. This data suggests quite lengthy persistence. Landcare Research New Zealand are currently evaluating the hepatic persistence of this compound in sub-lethally dosed rats compared with warfarin, coumatetralyl, and brodifacoum.

**Agency comment:** The residue data provided in Bullard et al. (1976) are included in the final document.

**WARFARIN SECTION**

(13) Page 68, Warfarin: With regard to comparative data on the toxicity of different anticoagulants to birds, in one study in which five anticoagulant-poisoned baits were fed to chickens (Lund 1981) brodifacoum was the most potent. It is noteworthy that warfarin baits had no effects on chickens, even after nearly a kilogram of bait had been eaten. [Lund, M. 1981: Hens, eggs and anticoagulants. *Int. Pest Control* **5**, 127–128.]

Table 1 Comparative effects of anticoagulants over 15 days in chickens

| Compound | Bait intake (g) | mg/kg | Mortality | Effect |
|---|---|---|---|---|
| Warfarin (0.025%) | 922 | 149 | 0/3 | none |
| Coumatetralyl (0.03%) | 594 | 107 | 2/4 | haemorrhage<br>loss of appetite from day 8 |
| Difenacoum (0.005%) | 611 | 19 | 2/4 | loss of appetite<br>haemorrhage from day 5 |
| Bromadiolone (0.005%) | 496 | 12 | 2/4 | loss of appetite<br>haemorrhage from day 6 |
| Brodifacoum (0.005%) | 362 | 10.5 | 4/4 | death from day 6 |

Table adapted from Lund (1981). No comparative data exists for other anticoagulant compounds, but it is noteworthy that the 5-day $LD_{50}$ for flocoumafen in feeding trials was 37 mg/kg for Japanese quail (*Coturnix coturnix*) and 1.7 mg/kg for mallard duck (Worthing and Hance 1991).

(14) Page 68, See Poche and Hach (2000): Wildlife primary and secondary toxicity studies with warfarin. *In:* John J. Johnston (*ed.*) ACS Symposium Senes 771: 181–196.

(15) Page 73, Re retention issue. See Appendix 1. There are additional publications to cite here.

**Agency comment:** The information provided for warfarin is included in the final document.

**ZINC PHOSPHIDE SECTION**

(16) Page 79, final paragraph: Use of English/spelling gets a bit loose here. In the sentence Sub-acute toxicity, put "the magnitude of the perturbations in clinical chemistry parameters was not reported":

**CHOLECALCIFEROL SECTION**

(17) Page 86: See the additional data re cholecalciferol primary toxic retention, and secondary poisoning attached.

**Agency comment:** The information provided for cholecalciferol is included in the final document.

## GENERAL COMMENTS

I strongly believe the tables on p. 105–109 should be in the main body of the text (minimise two or four to a page). Once the reader has evaluated these, numerous questions that are raised in reading earlier sections are immediately answered.

**N.B.** A 200-word summary or bullet point key points at the end of each section on individual compounds would be very useful, e.g.
Secondary poisoning studies with birds indicate low risk (<10%) in mammals moderate (30–40%) risk of causing death.

Attachment B highlights the need for field residue data in target species or from cage trials in rats, or both.

**Agency comment:** Appendix B [Appendix D in the final document] lists the incident data.

Finally, this report focus on the relative risk of wildlife (birds and mammals). In the regard the ranking is appropriate. However, veterinary toxicologists dealing with poisoned pets would be unlikely to concur with the low risk and implied acceptability of non-anticoagulant rodenticides. Anticoagulant poisoning is treatable. Non-anticoagulant poisoning can be difficult to diagnose and treat.

I have obtained some veterinary toxicologists' personal views regarding bromethalin, which may be of interest to the author. They indicate that they view bromethalin as "bad news". The rodenticide causes toxicosis in small animals that can mimic all sorts of central nervous system abnormalities up to and including head trauma, encephalitis, cervical and/or thoracolumn disk disease. Bromethalin toxicosis responds poorly to all treatments in most cases, apart from almost immediate (post-ingestion) detoxification of the gut. In contrast to anticoagulants that have effective antidotes, bromethalin is an unforgiving agent. Non-target and target animals can face a prolonged inhumane death.

Some veterinary toxicologists also view zinc phosphide with suspicion, believing that poisoning of non-target species is often not diagnosed.