RISK-BENEFIT CONSIDERATIONS IN EVALUATING COMMENSAL ANTICOAGULANT RODENTICIDE IMPACTS TO WILDLIFE

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ABSTRACT: Evaluation of the possible impacts of rodenticides on wildlife must be conducted in the context of risk-benefit considerations. Harmful introduced pests (e.g., commensal rats and mice) historically have required management around human habitation for economic and public health reasons. Disparate views of limited data have accumulated concerning the wildlife impacts resulting from commensal rodent control activities. The founding of the Rodenticide Registrants Task Force (RRTF), a trade association that includes all the major manufacturers and importers of anticoagulant rodenticide products (and bromethalin, a non-anticoagulant rodenticide) in the U.S., is described. The potential for anticoagulant dispersion in wildlife via primary and secondary routes is considered. Toxicology and pharmacokinetic studies are analyzed to obtain a better understanding of the biological and toxicological significance of low levels of rodenticide in animal tissue. A framework to address rodenticide impact to wildlife is presented. It is based upon the example of long-term cooperative efforts in England involving government, environmental, and manufacturer groups.

KEY WORDS: anticoagulant rodenticide, brodifacoum, bromadiolone, diphacinone, chlorophacinone, wildlife hazard, risk-benefit, residues, commensal rodents, Norway rat, house mouse, roof rat

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INTRODUCTION

Of the hundreds of exotic plants and animals introduced into the United States, few have done more damage and affected more lives than commensal rodents: the Norway rat (*Rattus norvegicus*), the roof rat (*Rattus rattus*), and the house mouse (*Mus musculus*). These small, agile, tough, and wary creatures have become the principal mammalian pests of the artificial urban landscape as well as many more natural areas (to the detriment of native wildlife). For a good general review of commensal rodents, see Corrigan (1997).

Economic and Disease Concerns

Commensal rodents live in and around human habitation, infesting homes, farms, commercial buildings, and food and feed stores, causing extensive damage. Burrowing by commensal rodents damages structural foundations, sidewalks, embankments, and other areas. They gnaw on electrical wiring and are responsible for fires and extensive physical damage to buildings and other structures. For a recent review of commensal rodent economic impacts, see Lund (1994).

Commensal rodents can spread many diseases to people, pets, and domestic animals (Gratz 1994). These diseases include plague, relapsing fever, leptospirosis, salmonellosis, Lyme's disease, rat-bite fever, rickettsial diseases (e.g., murine typhus), granulocytic ehrlichosis, and lymphocytic choriomeningitis. Rats and mice can spread leptospirosis and tapeworms to dogs and cats; brucellosis and foot-and-mouth disease to cattle; hog cholera and trichinosis to hogs; and salmonella, erysipelas, and fowl pox to poultry (Meehan 1984).

COMMENSAL RODENT CONTROL

Rodent control is often a difficult task, wherein a variety of tools, including integrated pest management (IPM) methods, must be used to obtain complete control. Due to the rapid reproduction rate of commensal rodents, controlling less than 90% of the population is essentially ineffective due to rapid replacement. As MacDonald and Fenn (1994) report, the growth curve of commensal rodents is such that populations left with more than about 10% of their maximum numbers will quickly rebound to pest status.

Alternatives to Rodenticides for Commensal Rodent Control

Few alternatives to rodenticides are available for the effective control of commensal rodents. Traps are a time-honored approach to rat and mouse control, as evidenced by the continual outpouring of new commercial designs (the "better mousetrap"). Traps vary in their effectiveness and utility. Their outdoor use is limited to protected placements to prevent injury to non-target animals and other disturbances that may prematurely trigger the trap. Glue traps are also popular in the U.S., although highly discouraged in some European countries due to humaneness concerns. Traps require frequent changing or servicing, and are best used inside buildings to intercept invading animals or remove individual rodents when populations are low.

Ultrasonic and electromagnetic rodent repellent devices have been commercialized for both residential and commercial uses as a means of preventing infestations of commensal rodents and other mammalian pests. No good

data exists to support the efficacy of these devices (Smith 1994). Several chemical repellents listing activity against rodents (among other animals) are available, but moving these pests to another area does not always lessen their impact.

Chemosterilants for commensal rodents have been evaluated but have met with practicable and commercial limitations (Brooks and Bowerman 1971; Ericsson 1982). Sterile rats can still consume and contaminate foodstuffs, damage materials, and bite children. The polygamous nature of rat populations means that low numbers of fertile males or females can still maintain significant population levels.

Sanitation and rodent-proofing (exclusion) are useful preventative measures to limit access to buildings or to food and harborage and are part of a comprehensive IPM control strategy. It is impossible, however, due to practical constraints in most commensal environments, to completely eliminate rodent access to structures; hence, direct methods must be used in most circumstances to obtain adequate control.

RODENTICIDES

By nature, mammalian toxicity is a requirement for rodenticides. Pharmacological selectivity to pest rodents has seldom been found for any candidate rodenticidal material. Rather, relative specificity is achieved through fine-tuning the selection of anticoagulant molecules to afford the greatest activity on rodents. Then, the much smaller body size of rats and mice, compared with most non-target predatory animals, provides for a useful dose differential. Further, protected placements (such as in tamper-resistant bait stations) aid in decreasing the risk of primary (direct) poisoning of wildlife.

Non-Anticoagulant Rodenticides

The earliest rodenticides, including red squill, arsenic, strychnine, and phosphorus, are all non-anticoagulant products. Subsequent products included 1080, 1081, ANTU, pyriminyl, and others. All of these earlier non-anticoagulant products (except for strychnine) have been removed from current use in the U.S. for various reasons including, for some, concerns of potential non-target hazards. The current non-anticoagulant products on the U.S. market include zinc phosphide, bromethalin, and cholecalciferol (Vitamin D3). Zinc phosphide has an acute (fast-acting) nature, leading to a bait shyness effect in survivors (learned aversion due to the rapid onset of symptoms). Calciferol products must be formulated at much higher levels than anticoagulants to be effective, and consequently show bait aversion both in the lab (Prescott et al. 1992) and field (Quy 1995).

First-Generation Anticoagulant Rodenticides

The development of warfarin and subsequent first-generation anticoagulants and their use, beginning about 1950, revolutionized rodent control in the U.S. and elsewhere (for helpful reviews, see Meehan 1984; Hadler and Buckle 1992; and Buckle 1994). Warfarin, diphacinone, pival, chlorophacinone, and fumarin are effective against rodents at very low concentrations (50 to 500 ppm). The delayed action caused by anticoagulants and the low active concentration prevented bait shyness and bait aversion.

However, the comparatively rapid elimination of these materials from the body necessitates consumption over a period of several consecutive days to maintain blood concentrations for the minimum four to five day period necessary for mortality to occur. Limited efficacy with house mice has often resulted due to their limited and sporadic feeding behavior and to the low intrinsic susceptibility of house mice to the early anticoagulants (Buckle 1994).

Resistance and Efficacy Concerns

First-generation anticoagulant resistance was first detected in Britain in the late 1950s (Boyle 1960) and was detected in the U.S. in the early 1970s (Jackson and Kaukeinen 1972). Resistance is genetic, and resistant individuals have been present in the population from the outset. Incomplete control allows for selection of resistant individuals. Studies established that resistance to first-generation products was a widespread problem in the U.S. (Jackson et al. 1975). Problems with house mice resistant to first-generation products were widely suspected, although only limited data is available for the U.S. (Ashton and Jackson 1984) and the U.K. (Prescott 1996).

Second-Generation Anticoagulant Rodenticides

Second-generation anticoagulant rodenticide development has been reviewed by Meehan (1984), Buckle (1994), and others. Specific compounds such as brodifacoum have also been the subject of extensive reviews (Kaukeinen and Rampaud 1986). Highly potent rodenticides such as brodifacoum and bromadiolone have unique advantages that allow much greater efficiency in rodent control programs in comparison to first-generation anticoagulants. Lower toxic doses help ensure control of sporadically-feeding commensal rodents and limits the duration that baits must be exposed to achieve pest population control. Control of rats and mice resistant to multiple-feeding anticoagulants can be achieved, while the major advantages of the earlier anticoagulants—delay before death and vitamin K antidote—are retained. Anticoagulant resistance continues to be a problem in many places around the world and has been demonstrated to occur with even some second-generation anticoagulants, while brodifacoum continues to be effective in achieving control in these resistance foci (Quy, MacNicoll, and Cowan 1988). Difethialone was introduced into the U.S. market in 1994. It is intermediate in activity between brodifacoum and bromadiolone. Extensive research projects have failed to make significant improvements upon existing molecules, and no new anticoagulant rodenticides, or non-anticoagulant ones, for that matter, are on the horizon.

Market Preference for Current Products

Data obtained from professional users in 1986 (Mix 1986) showed that over 98% of professional applicators were using either brodifacoum or bromadiolone products (or both) against commensal rodents, and that proportion is still true today. Similar proportions of product use are believed to be present in the over-the-counter (OTC) retail market.

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The total quantity of active ingredients of anticoagulant rodenticides that were produced or imported into the U.S. during 1996 and 1997 have been compiled by the RRTF (Table 1) (RRTF 1999a). These figures combine professional, OTC, and agricultural (farm commensal and field) uses. Agricultural uses, in particular, account for the larger amounts of chlorophacinone represented. Table 2 gives the quantities of active ingredient by market segment: professional (certified applicator), OTC (homeowner) and agricultural (commensal and non-commensal uses against field rodents such as ground squirrels). Diphacinone and chlorophacinone are sold for both commensal and field use, whereas brodifacoum and bromadiolone are sold only for commensal rodent control in and around structures. The OTC anticoagulant sales represents the smallest market segment with approximately 350 lb. (159 kg) of active ingredient used nationwide each year, yet there are 56 products with 24 formulations (15 of which include bittering agent) sold in this market sector. Table 3 shows these pounds of active ingredient expressed as the number of placements of end-use product. The OTC market is in excess of 40 million individual placements of 50 ppm formulated products, predominantly containing brodifacoum (RRTF 1999b).

Table 1. Pounds (wt.) active ingredient (A.I.) produced or imported in the U.S.

Active Ingredient	1996	1997
Diphacinone	486	608
Bromadiolone	233	164
Chlorophacinone	1,608	2,677
Brodifacoum	395	441
Total	2,722	3,890

RRTF 1999a

Table 2. Pounds A.I. (wt.) by market segment used in the U.S.

Market Segment	1996	1997
PCO	772	915
OTC	332	375
AG	1,663	2,457

RRTF 1999b

Table 3. OTC Containers (Placement Units)

Active Ingredient	1996	1997
Diphacinone	1,551,161	2,860,419
Bromadiolone	275,376	294,706
Chlorophacinone	21,552	18,360
Brodifacoum	40,895,724	44,144,456
Total No. Container/ Placement	42,743,813	47,317,941

RRTF 1999b

THE REGULATORY PROCESS

To achieve U.S. registration, extensive testing of candidate anticoagulant rodenticides was necessary, including with non-target species. For example, the NPIRS (National Pesticide Information Retrieval System Database; www.ceris.purdue.edu/npirs) indicates that all brodifacoum registrants submitted hundreds of study reports and documents between 1976 and 1998. These included 95 toxicology studies, 95 Product Chemistry Studies, and 56 Environmental Effects and Fate Studies. Tests were conducted on the active ingredient, on concentrates, and on the end-use formulated bait products. As part of the re-registration process, these studies have been re-reviewed by the U.S. Environmental Protection Agency (EPA).

RODENTICIDE REGISTRANTS TASK FORCE

The Rodenticide Registrants Task Force (RRTF) was organized in 1999 in response to the EPA's issuance of the Rodenticide Cluster Re-registration Eligibility Decision (RED). The EPA's re-registration process was concerned with three second-generation anticoagulants (brodifacoum, bromadiolone, and difethialone), four first-generation anticoagulants (warfarin, pival, chlorophacinone, and diphacinone), and three non-anticoagulant products (bromethalin, zinc phosphide, and cholecalciferol). Members of the RRTF are Bacon Products Corp.; Bell Laboratories, Inc.; California Department of Food and Agriculture; Consolidated Nutrition, L.C.; HACCO, Inc.; LiphaTech, Inc.; PM Resources, Inc.; Reckitt Benckiser, Inc.; Wilco Distributors, Inc.; and Zeneca Professional Products. The RRTF represents all of the rodenticide active ingredient registrants and over 80 percent of the consumer market sales volume of rodenticide products. The goals of the RRTF were to facilitate dialog between rodenticide registrants and the EPA and state regulatory agencies. Specifically, this facilitation was envisioned as follows: To combine expertise and share data, to work together to make product improvements, to consolidate label changes or facilitate other industry-wide changes as desired, to coordinate written comments to government agencies, to coordinate the development and submittal of data to address any information requirements or information gathering, and to coordinate dialog with other groups or

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associations having relevant databases.

One of the first goals of the RRTF was to coordinate a registrant response to issues in the RED regarding hazards to children. The RRTF's dialog with EPA, which is ongoing, is expected to result in the simplification of consumer rodenticide labels and educational outreach activities, both aimed at mitigating the accidental exposure of children to rodenticides.

WILDLIFE HAZARD CONCERNS

A prior review of potential wildlife hazard from anticoagulant rodenticides was published nearly 20 years ago (Kaukeinen 1982). At that time, the first-generation anticoagulants had been widely used against commensal and agricultural pests for over 30 years, and the second-generation products against commensal rodents for three or four years. At that time, no published reports of significant wildlife injury or death in the field from the application of first- or second-generation anticoagulant rodenticides could be found. Subsequent reviews (Colvin, Hegdal and Jackson 1988) discussed second-generation anticoagulant hazard findings only in terms of experimental agricultural trials (e.g., orchards), but presented no new hazard findings regarding commensal rodent control uses where baiting was conducted in and around structures, after approximately 10 years of heavy use of the second-generation anticoagulant rodenticides for commensal rodent control. Hegdal and Blaskiewicz (1984) had previously determined in a large-scale radio-telemetry study in New Jersey (U.S.) that commensal rodent baiting with brodifacoum in and around farms did not pose a significant risk to barn owls (*Tyto alba*). Barn owls were found to hunt away from farmsteads and to prefer voles (*Microtus* spp.) present in open fields. More recently, subsequent to the child hazard concerns, the EPA expressed an interest in considering whether wildlife hazard issues exist with the products under re-review in the RED process. The potential exposure to birds and mammals was considered via both primary (access to the toxic bait) and secondary (ingestion of poisoned rodents by predators) routes of exposure. The Agency reviewed data submitted as part of product registrations, as well as published papers and other data or information received.

Various papers and reviews comparing the acute toxicity of rodenticides to birds and mammals have been used as a basis for determining the relative risk of rodenticide active ingredients. These values can be misleading in terms of assessing potential wildlife hazards, as they are based on acute toxicity values in studies where the active ingredient was administered. And as Moore (1966) stated, "Pharmacological susceptibility bears little relationship to ecological vulnerability." It is necessary for non-target animals to have a likelihood of actual exposure for true risk to be present. Proper risk assessment considerations must take into account the end-use toxicant concentration and type of expected exposure. Formulated end-use anticoagulant rodenticide bait products are generally 50 ppm, or 0.005 percent (wt/wt.); therefore, the formulated material is expected to be four orders of magnitude (1/20,000) less acutely toxic than an equal weight of the active ingredient for the same species. Further, with anticoagulants, five-day chronic toxicity values may be more useful in assessing hazards (Ashton et al. 1987).

Primary poisoning requires bait to be exposed to wildlife and sufficiently palatable for a significant dose of the 25 to 50 ppm formulated bait to be ingested. Secondary routes of exposure result in a further dilution of anticoagulant in poisoned prey by approximately ten-fold (Merson et al. 1984). Figure 1 illustrates the progressive decrease or dilution of hazard (or increased margin of safety) associated with secondary risk to wildlife. Beginning with the active ingredient, hazard is sequentially lessened by dilution to end-use product, dispersed and protected placements, use in non-preferred predator hunting areas, and ingestion by non-preferred prey. If ingested, rodenticide in commensal rodent prey is initially eliminated rapidly with a fraction remaining bound in liver. Therefore, final risk of a predator taking a poisoned commensal rodent is low and further reduced by dilution with other, more normal prey items.

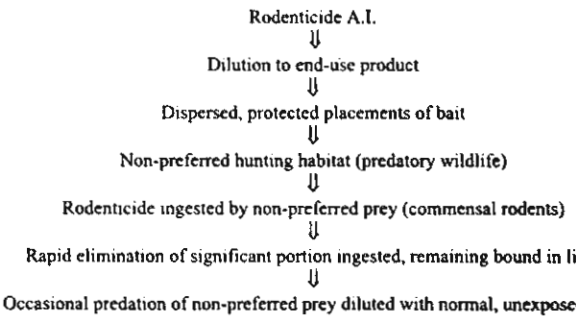

Figure 1. Gradient of dilution of relative hazard of rodenticides from A.I. to potential dietary exposure to predatory wildlife species.

In addition, rapid elimination of anticoagulants occurs through feces and urine, further decreasing the potential for secondary exposure. As Poche (1988) reported with bromadiolone, as much as 75% of the dose with rats was eliminated within four days after ingestion. What remains is tightly bound in the liver and slowly metabolized and released. Various studies have been conducted to demonstrate the toxicity of contaminated prey organisms to predator and scavenger species (Joermann 1998); however, these were non-choice dose/response studies designed to reach an end-point (i.e., result in toxicity). They are not representative of field exposure. The fact that captive animals could be killed with sustained consumption of sufficient anticoagulant-containing tissue is not surprising. Further, differences in the nature of the protocols for secondary-poisoning studies can lead to different results with the same materials. For example, Joermann (1998) cites unpublished research by Pank and Hirata that showed brodifacoum to have less effect on mongooses (*Herpestes auropunctatus*) than bromadiolone or chlorophacinone, although in other types of studies the ranking was reversed. The use of indicator species may also be misleading as, especially with birds, there appears to be species-specific differences (Joermann 1998) and differences by age in relation to duration of exposure

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(Shirazi et al. 1994). The relative sensitivity of an indicator species to different exposure regimes in a particular use pattern might give relative differences and thresholds, if effects of diet, time of year (breeding, molting), and relative stress on the animals could be taken into account. With raptors, regurgitation of pellets appears to be a major route of anticoagulant excretion during the first day or two after feeding on contaminated tissue (Newton et al. 1994).

Although not reflecting current U.S. registrations, published information is available on broadcast field uses of brodifacoum and bromadiolone. These data are derived from several sources, including experimental research trials evaluating brodifacoum for orchard vole control (Merson et al. 1984; Hegdal and Colvin 1988), and extreme efforts to control introduced exotic species (including mammalian predators) in New Zealand (Eason et al. 1996; Eason and Murphy 1999; Rammell et al. 1984), or control of voles in Europe with bromadiolone (Grolleau et al. 1989; Berny et al. 1997). These studies are not relevant to current-use patterns for any second-generation rodenticides in the U.S. They involve different formulations, concentrations, and methods of dispersal (including by aerial broadcast), and should not be considered in estimating risk from commensal uses in the U.S. In the U.S., all second-generation anticoagulants (brodifacoum, bromadiolone, and difethialone) are only registered for use against commensal rodents in and around structures, and broadcast uses are prohibited.

Wildlife Mortality Incidence Schemes

Various sources list "rodenticide incidents" involving birds and mammals (Stone et al.1999; NWHC 1998ab; NWHC 1999; EPA 1999; Hosea 2000). The limited nature of these data complicates their evaluation. Details of specific incidents are often very limited; thus, it is difficult to assess their relevance or gauge their significance. For the California data (Hosea 2000), most carcasses were recovered near urban development. Canine species included gray and red foxes (*Vulpes vulpes*) and coyotes (*Canis latrans*). A significant number of the latter was among pest animals live-trapped and in apparent good health before euthanasia (Hosea 2000). Felines reported were a bobcat (*Lynx rufus*) and a mountain lion (*Felis concolor*). Various hawks and owls were also recovered, as well as raccoons (*Procyon lotor*) and gray squirrels (*Sciurus carolinensis*). Fifty-eight cases possibly involving anticoagulants were investigated by the California Department of Fish and Game (CDFG) between 1994 and 1999, and residues of anticoagulants were found in 38 cases (66%). Since clinical signs of coagulopathy were found in only 10% to 20% of the carcasses, the impact of low-level anticoagulant residues on the health of the remaining 80% to 90% of the animals recovered could not be determined. It was noted that additional possible mortality factors in the animals found dead included collision with vehicles or structures, bite wounds and poisoning with organophosphates or lead (Hosea 2000). Other observations were reported from New York (Stone et al. 1999), where some 55 carcasses were analyzed for anticoagulants between 1971 and 1997, and anticoagulants were found in about 80% of these cases. Again, a definitive cause of death and the role of the generally low residues of anticoagulants could seldom be attributed with individual animals examined.

Most toxicologists would agree that incident data are a poor forensic tool in determining causality. Typically, the route of exposure and the health and sensitivity of individual animals is unknown. Incident data can be used most effectively to evaluate trends in causative factors, but sufficient knowledge of populations in question (e.g., alternate potential sources of mortality) is needed to assess the relative importance of specific diagnostic findings. The current data reported in the U.S. regarding wildlife incidents do not represent systematic searches or widespread recoveries. Instead, they are limited to recovery and analysis or autopsy (or both) of carcasses observed and reported, generally from roadways or other traveled areas (NWHC 1998b). Proponents of a greater than demonstrated incidence of rodenticide mortalities (i.e., those believing only a small proportion of incidents is found and reported) state that the limited reporting, as well as high rates of carcass loss and decay, preclude any accurate assessments of populations effects. Collection of carcasses from sites of mortality as the result of disease or poisoning has been shown to be variable due to different removal (disappearance) rates and ease of detectability of the carcasses. Removal and detectability rates depend on the habitat (agricultural field, marsh, grassland, or forest) and the presence of scavengers or predators (Tobin and Dolbeer 1990; Linz et al. 1991). In Good Laboratory Practice (GLP) studies with carbamate and organophosphate insecticides/nematicides, carcass removal rates much lower than 70% per day have been documented. These studies involved a range of crops and regions, from potatoes in the Pacific northwest, citrus groves in Florida, cotton fields in California, and tobacco in North Carolina (Hobson et al. 1988, 1991). As Fisher (1990) states, estimation of mortality rates for wildlife populations based on carcass retrieval is difficult, and other methods of estimating population effects may be more useful in determining the significance of mortality rates in wildlife populations. Banding recovery studies, systematic surveys based upon sightings, calls, or nests, and analyses of scats (birds and mammals) and regurgitated pellets from raptors (Gray et al. 1994a) may have merit. Non-destructive field sampling might involve analyses of blood samples of trapped animals (Walker 1992).

In July 1999, the CDFG recommended to the California Department of Pesticide Regulation (CDPR) that brodifacoum be placed in a re-evaluation process, based upon the incident data it had generated (Hosea 2000). CDPR enacted this review formally in February 2000, and as of this writing the review is ongoing for an unspecified period. The limited California incident data from CDFG do not allow the determination of what trends or areas of concern might be represented with particular species (none of which are endangered), or what problems might exist in particular, geographic areas or habitat types. The "wildlands" referred to by Hosea (2000) as the recovery sites of some animals include drastically altered landscapes such as grazing land. Many of the recoveries could indicate individual animals that died from multiple factors including those unrelated to anticoagulants. Further, there is no way to determine

scientifically whether a typical analytical recovery indicates a lethal or asymptotic anticoagulant level for that individual, or whether the route of ingestion was primary or secondary.

Potential for Rodenticide Abuse and Misuse Causing Wildlife Hazards

Finally, the role of misuse and abuse (i.e., off-label use) in these incidents must be considered in understanding the importance of individual incidents. Pesticide abuse can be defined as the criminal (intentional) misuse of pesticides for the purposeful damage of wildlife or other non-target animals. Pesticide misuse can be defined as the unintentional, accidental, or careless use of pesticides causing damage to wildlife. Misuse may involve lack of adequate consideration or safeguards to reduce potential application hazards. The California and New York data suggest that abuse and misuse may be factors in some of the residues observed. Independent investigations in Southern California revealed that police departments had recommended second-generation anticoagulants for the control of coyotes in neighborhoods (Baker 2000). Difficulties in the control of ground squirrels (*Spermophilus* spp.) or of roof rats in vegetation away from structures suggest the likelihood that some persons in California (and elsewhere) may have utilized brodifacoum or bromadiolone for these uses, in violation of the product labels. Recoveries of residues of coumatetralyl in New York wildlife also indicate misuse or abuse, since this material is not sold in the U.S. Abuse and misuse of anticoagulant rodenticides have been reported elsewhere. Investigations in the U.K. showed that a significant proportion (86%) of 202 observed mortalities of wildlife investigated between 1993 and 1996 as part of the Wildlife Incident Investigation Scheme (WIIS) of the U.K. Department of Agriculture was caused by pesticide abuse (Buckle et al. 2000). Investigations by the WIIS for all pesticide-poisoned animals between 1994 and 1996 found that negligent use of pesticides was judged to account for 76 out of 408 suspected incidents in England (Barnett and Fletcher 1998).

Mortality Rates Versus Quantities Used

The reported wildlife mortality rate for rodenticides is low in proportion to the amount of use. The incident data for the two states in which there are reported or alleged wildlife mortalities from anticoagulant rodenticides —California and New York—was compared to the estimated use rate of anticoagulant rodenticides in those two states (see Table 4).

Rodenticide use in New York and California can be estimated by applying the percentage of population in each state—12% in California and 6.7% in New York (U.S. Census Bureau 1999)—to the total rodenticide use (RRTF 1999a). These data illustrate the low number of reported wildlife incidents relative to the large amount of formulated product and the number of containers (placements) used in these states for two recent years.

RISK/BENEFIT CONSIDERATIONS

EPA is required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to consider the benefits of rodenticides. Specifically, FIFRA Section 3(c)(5) provides that EPA "shall" register a pesticide if, among other criteria, "when used in accordance with widespread and commonly recognized practice [the product] will not generally cause unreasonable adverse effects on the environment" (FIFRA § 3(c)(5), 7 U.S.C. § 136a(c)(5)). "Unreasonable adverse effects" are defined

Table 4. Comparison of rodenticide use with the number of wildlife incidents.

State	Year	Pounds of Active Ingredient[a]	Pounds of Formulated Product[b]	Containers/ Placements[c]	Reported Wildlife Incidents
California	1996	333	6,600,000	5,640,000	6[d]
	1997	475	9,533,333	6,120,000	19[d]
New York	1996	181	3,600,000	3,149,000	13[e]
	1997	259	5,200,000	3,417,000	10[e]

[a]The pounds (wt.) active ingredient (A.I.) for each state and year were estimated by multiplying the total A.I. sold annually by the proportion of the total population in each respective state.
[b]Similar to the pounds A.I., the pounds formulated product for each state and year were estimated by multiplying the total pounds sold annually by the proportion of the total population in each respective state.
[c]The number of containrs/placements for each state and year was estimated by multiplying the total number of containrs sold annually by the proportion of the total population in each respective state.
[d]Hosea (1999).
[e]Stone et al. (1999).

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as "any reasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits" (FIFRA § 2(bb), 7 U.S.C. § 136(bb)).

A WAY FORWARD

The extensive data available on anticoagulant rodenticides under controlled conditions can provide useful information to extrapolate to wildlife hazard potential. Further, the similarity of anticoagulant rodenticides and the occurrence of various ingredients in the residue analyses from California and New York suggests that these issues can usefully involve consideration of a broader database than that associated with just one active ingredient (e.g., brodifacoum). Finally, federal EPA and state initiatives concerning wildlife hazard from rodenticides should be coordinated so that any resolution can be reached simultaneously on a national basis. As part of the dialog to investigate these issues, there are several important topics to consider: the significance of anticoagulant residues in relation to toxicokinetics, factors in the recovery of carcasses and the pathology information derived from them, the number of carcasses with residues versus the magnitude of use of the anticoagulant products, and a risk-benefit analysis of using these rodenticides to control harmful commensal species.

Toxicological Significance of Anticoagulant Residues

The presence of low-level residues of anticoagulant rodenticides in wildlife tissues and other environmental matrices is readily quantifiable using current analytical techniques (O'Bryan and Constable 1991). While half-lives vary, all anticoagulant rodenticides exhibit a biphasic clearance (Figure 2) with a rapid initial phase and a slower terminal phase (WHO 1995).

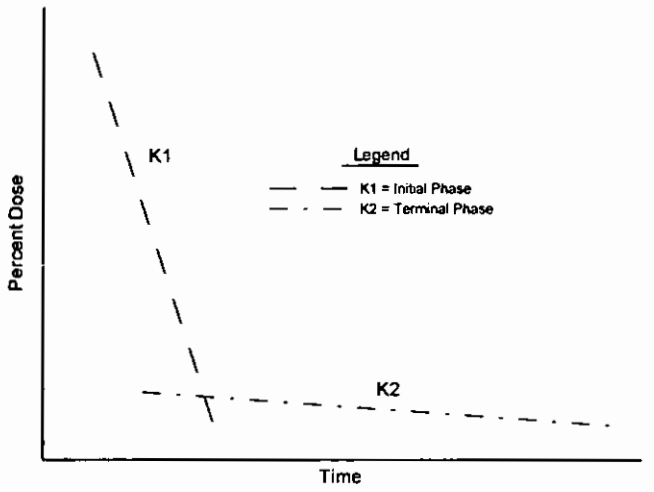

Figure 2. Biphasic elimination curve (conceptual).

This is indicative of two essentially independent processes. The first is a rapid clearance from the plasma and some shallow compartments within a few days, followed by a much slower elimination from the saturable, high-affinity binding site in the liver (WHO 1995). The half-lives of each phase vary with the specific anticoagulant. Warfarin retention may be limited to a few days, but half-lives of most second-generation anticoagulants (and many first-generation anticoagulants) exceed 100 days for the terminal phase (WHO 1995). For example, brodifacoum has a reported initial half-life of one to four days, and a terminal half-life of 128 days or more (O'Bryan and Constable 1991). The number of data points and manner of calculation of anticoagulant half-life can affect the end results, and various values have been reported in the literature for the same compound (Lechevin and Vigie 1992).

Parmar and co-workers (1987) have shown that, in the terminal phase of clearance, anticoagulants are bound in the liver to a capacity-limited site and are very slowly released and excreted as the parent compound (Parmar and Batten 1987; Parmar et al. 1987). Huckle and co-workers (1988) reported that induced coagulopathy from several second-generation anticoagulants did not occur until this binding site had been saturated. Furthermore, binding to this saturable site in the liver appears to be independent of initial dose exposure (Gray et al. 1994b), i.e., since the site has a limited capacity, measuring the liver fraction cannot determine the relative magnitude of the initial exposure. In addition, in the terminal phase, liver residues do not appear to be associated with coagulopathy, based on radio-labeled studies (Parmar et al. 1987; Huckle et al. 1988). Persistent coagulopathies may reflect larger ingested or repeat doses that circulate in the blood because liver binding sites are full. These observations may be very important in interpreting the toxicological significance of residues found in the livers of wildlife species.

Gray and co-workers (1994b) found that owls in the wild survived with 0.7, 0.15, or 0.5 mg/kg of brodifacoum, difenacoum, or flocoumafen, respectively, in the liver. Liver residues exceeded these levels in all owls that died, indicating a "threshold of toxicity." This threshold varies with different second-generation anticoagulants (Gray et al. 1994b) and appears to be consistent at approximately 0.7 mg/kg liver for brodifacoum, after both field and laboratory exposures, for birds (Gray et al. 1992, 1994b; Newton et al. 1990; and Edwards et al. 1988) (Table 5a) and mammals (Edwards et al. 1988). Furthermore, the mammalian data is supported by observations reported by the CDFG (Hosea 1999). In a Pesticide Laboratory Report number p-2051 (Feb 1999), CDFG reported euthanizing ten apparently healthy coyotes and analyzing the livers from five of these ten individuals. All ten were necropsied. Reported residues of brodifacoum, and sometimes bromadiolone, ranged from 0.23 to 0.46 mg/kg liver and 0.07 to 0.36 mg/kg liver, respectively. However, "... all animals appeared to be in good to excellent body condition," and the necropsy showed "no symptoms ... which would indicate anticoagulant toxicosis in any of these animals" (Hosea 1999). This data supports the threshold concept for mammalian wildlife species exposed to brodifacoum.

California and New York incident data were analyzed utilizing this threshold of 0.7 ppm brodifacoum in liver, and the results are presented in Table 5b. Applying this

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Table 5a. Toxicological significance of anticoagulant residue—magnitude of liver residues (brodifacoum in owls).

Disposition	Residue	Reference
Surviving	0.7 ppm	Gray et al. 1992
Dead	1.7 ppm	Gray et al. 1992
Dead	0.63-1.25 ppm	Newton et al. 1990

Table 5b. Magnitude of residues associated with mortalities.

	Cases	Mean Definition	Range
California Fish & Game (Hosea 1999)	31/32	0.15 ppm	<0.7 ppm (0.01-0.66)
	1/32	3.9 ppm	>0.7 ppm --
New York (Stone et al. 1999)	32/41	0.44 ppm	<0.7 ppm (0.01-0.7)
	9/41	2.17 ppm	>0.7 ppm (0.93-4.6)

threshold to the data from both states indicates that for the majority of animals included in incident reports, levels of brodifacoum are below that expected to cause acute mortality (Table 5b). In the analysis of ten coyotes (discussed above), the conclusion of the unpublished CDFG report was: "the residue concentrations in these otherwise healthy animals may suggest that background levels of anticoagulant rodenticides are found in urban carnivores ..." (p-2051, Hosea 1999). However, in other incident reports by CDFG, these and lower levels of second-generation anticoagulants are cited as diagnostic of the anticoagulant as the causative agent of mortality (Hosea 1999). Inconsistencies suggest the difficulty of ascribing causality in these cases, and the value of agreed protocols for pathology and chemical analysis (Brown et al. 1996). Detection of low-level residues may represent the slow terminal phase of clearance with residues sequestered in the liver, and must be carefully interpreted with respect to any forensic, diagnostic, or toxicological significance. Long-term anticoagulant feeding studies in rats, such as with diphacinone for example, failed to find consistent effects on clotting times or general health and feeding behavior at levels of 0.03 to 0.5 ppm over 90 days of continuous feeding (Elias and Johns 1981).

All of the second-generation compounds have similar persistence, and liver retention of many first-generation anticoagulants is comparable, although the half-lives are shorter (Parmar et al. 1987; Huckle et al. 1988). Thus, relative residue findings in multi-causative analyses may reflect product popularity. Furthermore, when liver residues of brodifacoum or other anticoagulants are found to be significantly smaller (e.g., 1/10) than the capacity of the saturable site in the liver (e.g., 0.7 mg/kg), this indicates that no recent exposure had occurred. The liver binding site has a high affinity for the anticoagulants which are bound preferentially from the plasma (at a 20:1 ratio). The terminal phase half-life is so long (e.g., 128 days for brodifacoum), that a residue of 0.07 mg/kg (1/10 the saturation level) or less of brodifacoum, for example, suggests that the animal has not been exposed for well over 128 days. More frequent re-exposure to significant levels of the same, or a similar anticoagulant (second-generation compound) would be expected to result in rapid re-saturation and lead to characteristically high levels in the liver. Therefore, if lower levels of anticoagulant in the liver indicate infrequent and/or low levels of exposure, such levels are best considered a marker of exposure, rather than as a diagnostic tool to determine the cause of mortality.

The low residue levels generally reported by Hosea (1999) and Stone (1999) are liver residues and, unless a significant exposure recently occurred, the liver residues are the only significant residues in the body (Parmar et al. 1987; Huckle et al. 1988). Since the liver in rats and mice generally ranges from 10% to 15% body weight (Hayes 1984), the whole body residue of brodifacoum or other anticoagulant would be approximately an order of magnitude lower than that reported in the liver. These residues of <0.07 mg/kg liver are two orders of magnitude, or more, lower than reported LD50s and lethal dietary exposures for wildlife species reported in the literature (Godfrey 1985; WHO 1995), indicating that secondary hazard is low for liver residues of <0.7 mg/kg liver.

The veterinary community generally appears to regard blood or sera residue levels to be of most value for diagnostic and therapeutic purposes in cases of treating non-target animal poisonings. For example, DuVall et al. (1989) recommend that veterinarians discontinue therapy when serum levels of brodifacoum in dogs and cats drop below 0.5 ppb, even though much higher levels may be found in the liver. High serum levels seen in animals

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requiring treatment were considered to reflect a recent, massive dose. These same authors note the difficulty of diagnosis from pathological examinations alone, because coagulopathy has many other potential causes besides anticoagulants, including ehrlichiosis, infectious canine hepatitis, heat stroke, and many other conditions.

Versus Other Mortality Causes

Compared to other sources of wildlife mortality, rodenticide toxicity incidents are extremely low. For the period from July 1998 through March 1999, the National Wildlife Health Center (NWHC 1998ab, 1999) of the U.S. Geological Survey reports for 1998 and 1999 (three quarters) indicated causes of avian mortalities as follows: 3026 from disease, 99 from chemicals or agricultural chemicals, and 8 individual animals representing a single incident with a rodenticide. Diseases accounted for the majority of deaths (e.g., botulism, salmonellosis, and avian cholera).

Data compiled from federal, state, and independent research facilities indicate there are three leading causes of mortality to avian and mammalian wildlife: disease (NWHC 1998ab,1999; Long 1998), transportation collisions (Julian 1997), and electrocutions and collisions with television towers and other man-made structures (Trapp 1998; California Energy Commission, 1995). Highways and other linear developments are known to impact the ecology of wildlife species, specifically small and large mammals and birds. Over the past 30 years, avian collisions with television and other towers have increased (Trapp 1998; California Energy Commission 1995). Reports include single bird collisions with radio towers and/or wires to reports of over 1,000 birds killed during a single night. Authorities have estimated that about 100 million birds die annually from striking residential windows in winter (Dunn 1993; Klem 1991). Finally, starvation and parasitism are also common causes of death for wildlife (Barr 1998).

These comparisons put into perspective the exceedingly low number of mortalities associated with rodenticides. Granivorous birds and small mammals have high reproductive potential and high rate of natural and anthropogenic mortality. For example, one to two million feral and rural cats in Wisconsin are estimated to kill millions of birds per year (Coleman and Temple 1996). Observed wildlife mortalities related to rodenticides do not, on a relative basis, seem to represent a significant contribution to the overall mortality rate of these wildlife species.

Impact of Label Restrictions

For pesticide products, the label is the law. Considerable precautions already exist on second-generation anticoagulant labels in regard to wildlife and non-target animals. For example, brodifacoum product labels state: "This product is toxic to birds, fish, and wildlife. This product can pose a secondary hazard to birds of prey and mammals. It is a violation of Federal law to use this product in a manner inconsistent with its labeling. Do not expose children, pets, or other non-target animals to rodenticides. To help prevent accidents, apply bait out of reach of ... non-target wildlife or in tamper-resistant bait stations. Dispose of unused, spoiled, and unconsumed bait. For use in and around structures." And finally, "Do not broadcast bait." However, the potential of further label statements to mitigate wildlife hazard is unknown. Investigations of pesticide misuse and abuse by state and local agencies and the publicity around fines or other penalties applied to offenders may have greater impact in lessening wildlife incidents.

Example of an Integrated Scheme from the U.K.

A recent presentation at an international meeting (Buckle et al. 2000) concerned a synthesis of available and published findings in the U.K. regarding the hazard to barn owls from anticoagulant rodenticides. This represents a good example of the useful integration of bird survey data with pesticide usage reports and with wildlife incident investigation schemes. Only within such a framework—comparing large databases—can true mortality effects be accurately assessed.

Various U.K. barn owl surveys indicated a decline in owl numbers during the 19th century and much of the 20th century, but the species appear to no longer be in rapid decline. There was no evidence that rodenticide poisoning had a significant impact on barn owl numbers in the U.K. (Wyllie 1995). These data were collected during a period of extensive and stable anticoagulant rodenticide use (including second-generation products). The principal causes of owl mortality were found to be starvation and trauma.

Increased Wildlife Monitoring Needed

Much more meaningful data must be collected in the U.S. in order to draw inferences for regulatory purposes. Only a combined effort of government, private industry, and conservation groups can effectively establish how best to reduce significant deleterious effects to wildlife, especially predatory birds and mammals. Perhaps education programs, and certainly more aggressive field investigations and prosecution of pesticide abusers, will be important steps. Published accounts co-authored by rodenticide manufacturers and government agencies in the U.K. might represent a possible framework for future efforts (Brown et al. 1988).

SUMMARY

A careful review of the available information regarding wildlife effects from anticoagulant rodenticides suggests that its significance has been overestimated. The low-level residues found in livers of some recovered wildlife carcasses (including apparently healthy, trapped animals) represent a marker indicating some prior exposure, but these findings cannot generally be credited as indicative of mortality-causing effects. Rodenticide misuse and abuse are likely important aspects of the residues of anticoagulants found in many of the wildlife carcasses. Improved necropsy methods, standardization of pathology investigations, and analysis for anticoagulants in blood (rather than only liver) would give better indications of causes of death. The observed wildlife contamination by anticoagulants must be viewed versus the magnitude of anticoagulant rodenticide product use. The relative incidence of specific anticoagulants appears to follow closely the known market share of these various products. Commensal rodents are harmful pests

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that are injurious to people, pets, domestic animals, commodities and other goods, structures, and wildlife; thus, rodenticides are highly beneficial to society. A greater significance of demonstrated wildlife effects needs to be documented before any mitigation measures are instituted that could limit the ability of professional applicators, farmers, and homeowners to provide protection against these harmful pests.

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