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Assessing individual and population-level effects of anticoagulant rodenticides on wildlife

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Abstract: Anticoagulant rodenticides have been detected in many species of wildlife worldwide. However, the origins, exposure pathways, and effects of this exposure are not well understood. To accurately characterize the risks to wildlife from rodenticide use, better information is needed regarding the proportion of populations being exposed, what proportion of individuals in populations are affected, and in what ways. The relationship between anticoagulant rodenticide concentrations found in wildlife and the rate of mortality or illness have been the subjects of much research. Residue levels observed in liver and whole-body analyses vary and overlap extensively among apparently healthy asymptomatic individuals and sublethal and lethal cases. Results from laboratory studies also show there can be wide variability in lethal and sublethal effects among and within taxonomic groups. Correlating the sublethal and reproductive effects observed in laboratory studies with realistic exposure scenarios and effects in the wild is needed to improve risk assessments. For species with limited numbers or declining populations, a critical question yet to be answered is if the rodenticide exposure documented in individual animals inhibits population growth or contributes to population declines by lowering survival and reproductive success. This information is essential to the regulatory agencies that must weigh the risks and benefits of rodenticide uses and identify restrictions that are effective in reducing risks to wildlife.

Key words: Anticoagulant rodenticides, lethal effects, pesticide residues, regulations, sublethal effects, wildlife

Anticoagulant rodenticides are widely used, toxic to a broad range of taxa, and persistent in many organisms. Despite mitigation measures implemented by the European Union, United Kingdom, U.S. Environmental Protection Agency (US EPA) and the state of California, USA to reduce exposure, current research on the environmental effects of rodenticides has continued to document their occurrence in wildlife (Gabriel et al. 2018, Shore et al. 2018).

The lack of effectiveness of mitigation measures (California Department of Pesticide Regulation 2019) demonstrates the need for more information on how exposure occurs. Furthermore, existing methods for conducting risk assessments for anticoagulant rodenticides have been inadequate at predicting the occurrence of physiological effects in individuals in wild populations.

Literature synthesis

This paper summarizes the state of knowledge and data gaps discussed during the Symposium on Anticoagulant Rodenticide Residues in Wildlife held in conjunction with the Twenty-Seventh Vertebrate Pest Conference, Rohnert Park, California. The symposium covered 3 lines of inquiry: (1) presence and prevalence of anticoagulant rodenticides in wildlife, (2) pathways of anticoagulant rodenticide exposure in wildlife, and (3) the impacts of rodenticide exposure on wildlife.

The ranges of approaches and methods presented by the symposium participants, how their data differed or were in agreement, and the conclusions they drew improved understanding of the issues while also reinforcing the need to accelerate progress in identifying and addressing knowledge gaps.

Presence and prevalence of anticoagulant rodenticides in wildlife

Initial awareness of hazards to nontarget wildlife from anticoagulant rodenticides emerged in the 1970s and 1980s (Kaukeinen 1982, Godfrey 1985, Colvin et al. 1988). When people have tested animals for rodenticide residues after known applications, residues have been detected (Winters et al. 2010, Salim et al. 2014). Subsequent studies largely focused on documenting exposure (Eason and Spurr 1995, Berny 2007, Albert et al. 2010, Sánchez-Barbudo

Figure 1. Anticoagulant rodenticide residues have been detected in a wide range of mammals including coyotes (*Canis latrans; photo courtesy of N. Quinn*).

et al. 2012). Anticoagulant rodenticides have been found in a broad range of taxa in a number of countries, although there appears to be a geographic bias, with most studies being conducted in North America, Europe, and New Zealand.

There have been detections of anticoagulant rodenticides in marine species (Pain et al. 2000, Primus et al. 2005, Pitt et al. 2015), invertebrates (Spurr and Drew 1999, Bowie and Ross 2006, Elliott et al. 2014), and in reptiles (Pitt et al. 2015, Rueda et al. 2016). Anticoagulant residues have been detected in a number of bird species, including raptors (Newton et al. 1990, Stone et al. 2003, Murray 2011, Langford et al. 2013), passerines (Pryde et al. 2013, Elliott et al. 2014), waterfowl (McMillin and Finlayson 2010), and game birds (Ruder et al. 2011). Residues have also been detected in a wide range of mammals (Figure 1). These detections included predators (Shore et al. 1999, Riley et al. 2007), and insectivorous (Dowding et al. 2010) and herbivorous mammals (Eason et al. 2001).

One of the main limitations with interpreting exposure results is that they must be placed in the context of populations. By not reporting the number of animals tested as a proportion of the total population, studies of detections in individual animals do not provide a population-level assessment of exposure. Anticoagulant rodenticide residues are often detected through studies on threatened or endangered species, charismatic megafauna, or on spotlight species, especially raptors. These studies are not random samples of populations; the methods by which individuals are selected for rodenticide testing introduce inaccuracies due to multiple and contradictory factors.

Testing only mortalities and symptomatic individuals and not those that appear to be healthy does not measure the actual proportion of the population that is exposed. This type of non-random sampling design, which is based on the greater likelihood of detection of symptomatic individuals, also does not accurately assess the proportion of exposed animals that are affected by the exposure because animals unaffected by exposure are not included at all. If sublethal effects are present, they may be difficult to detect, and therefore these animals are not selected for testing, and are also not included in the results.

Animals that have succumbed to rodenticide intoxication are also underrepresented because they may not be discovered. Carcass detection studies have found that even when searches are conducted for carcasses known to exist (e.g., placed by a researcher for study), a percentage will never be found due to scavenging, location in remote and inaccessible areas, or size or coloration that renders the carcass inconspicuous (Vyas 1999, Elliott et al. 2008). Finally, public reporting of wildlife mortalities in general is limited both by the detectability of carcasses as well as uncertainty as to whether the incident should be reported and to whom it should be reported, lack of timely reporting, and indifference (Vyas 1999).

Exposure pathways

Detailed information about rodenticide exposure pathways is essential for designing effective mitigation measures (Figure 2). Modifications to how rodenticides are applied are unlikely to be successful at reducing nontarget exposure if it is not understood how rodenticides travel from the point of application to nontarget species. Studies examining the initial stages of rodenticide transfer from known agricultural or commensal application sources have documented the widespread transfer of rodenticides into both target and nontarget species in the surrounding areas (Silberhorn et al. 2003, Tosh et al. 2012, Vyas et al. 2013, Elliott et al. 2014, Geduhn et al. 2014). The bait in these studies was applied according to legal methods (except as noted in Tosh et al. 2012), in many cases by the researchers themselves, yet

Figure 2. American kestrels (*Falco sparverius*) are being studied to improve understanding of the effects of anticoagulant exposure on raptor populations (*photo courtesy of R. Buechley*).

the rodenticides were still detected in a wide range of nontarget taxa, including invertebrates, small mammals, passerines, and raptors. This clearly demonstrates that the processes by which the rodenticide travels beyond the point of application are outside of the control of the applicator. It is therefore not surprising that mitigation measures based on the assumption that professional applicators will apply rodenticides more safely (e.g., EPA 2008, California Department of Pesticide Regulation 2013) have not resulted in a measurable decline in wildlife exposures (van den Brink et al. 2018).

Wildlife may be exposed to anticoagulant rodenticides through a number of pathways, which vary considerably in their complexity. Constructing an exposure pathway requires accurate information about the source of the rodenticide, the diet and foraging behavior of each species, and the true prevalence of exposure within the populations. Rodenticides are applied in agricultural and field sites (e.g., fallow cropland, around crop borders, in and around orchards and tree nurseries, rangeland, dikes, parks, and landscaping) and in commensal sites (in and around buildings) in urban, suburban, and rural areas. In many countries, specific active ingredients can only be legally applied for specific sites, uses, and against particular species.

First-generation anticoagulant rodenticides (FGARs) are mostly used to control field rodents in agriculture and sites away from human habitation. Second-generation anticoagulant rodenticides (SGARs) are limited to application in and around structures to control commensal rats (*Rattus* spp.) and mice (*Mus* spp.), with the exception of bromadiolone, which has field uses outside of the United States. The FGARs are also used to control commensal rodents in and around structures (Figure 3).

From the point of application, exposure to the rodenticide can be primary, secondary, tertiary, or at further levels. Primary exposure is defined as the direct consumption of the rodenticide; secondary exposure results from the ingestion of prey that has fed on the rodenticide; tertiary exposure occurs when an organism consumes prey that has predated on an organism that has been exposed, and so on. An individual animal can be exposed at more than a single level and from different rodenticide sources over a period of time. Residues of multiple anticoagulant rodenticides, including both FGARs and

Figure 3. Second-generation anticoagulant rodenticides are limited to application in and around structures to control commensal rodents (*photo courtesy of N. Quinn*).

SGARs, are often detected in individuals (Riley et al. 2007, Gabriel et al. 2018).

For some nontarget wildlife species, there does not appear to be a connection with the target species and/or the site or method of bait application. The original source(s) of the rodenticide are often unknown; the nearest identified source may be distant, outside of the species' habitat or the individual's home range (Berny 2007). Some primarily exposed species are not known to enter bait stations or otherwise have had no obvious access to bait (seed-eating birds, rabbits and hares; S. McMillin, California Department of Fish and Wildlife, personal communication). Some species that are secondarily exposed through predation on rodents, or exposed at the tertiary level or further, such as mesopredators like coyotes (*Canis latrans*) or apex predators like mountain lions (*Puma concolor*), do not prey on the target rodent species, leaving their route of exposure unknown. The delayed toxicity of anticoagulant rodenticides and their persistence within tissues can result in contaminated rodents being found within and adjacent to the treated area weeks or months after bait application (Sage et al. 2008, Tosh et al. 2012, Geduhn et al. 2014).

The low number of publications on exposure pathways reflects the difficulty in studying them. The methods employed are indirect and generally involve working backwards from the exposed species to many potential application sources within a broad area. Scat analyses for anticoagulant rodenticides are an example of an indirect method that provides only limited information due to the low likelihood of detection of the scats themselves and the likelihood of misidentification of the depositing species (Morin et al. 2016). Camera and direct visual observations of nontarget species' interactions with bait or the target species (Vyas et al. 2013, 2017; N. Quinn, unpublished data) provide information at the source of the rodenticide application that can be used to modify application methods. Biochemical analytical methods, such as the use of stable isotopes in custom-marked rodenticide baits, could be utilized to trace the rodenticide from a point source through food webs.

A limitation of the current state of knowledge for exposure pathways is that the studies conducted are qualitative and therefore unable to predict the likelihood of exposure for individuals, the proportion of a population that is exposed, and the effect on survivorship or other demographic parameters as a result of the exposure. New approaches to detect and quantify the proportion of applied rodenticide that travels through specific routes to each nontarget species are urgently needed, along with more emphasis on developing probabilistic models of exposure and its effects.

Effects of anticoagulant rodenticide exposure

Rodenticide exposure to wildlife is a multi-faceted issue that encompasses more than whether or not an individual has been exposed. Data on the magnitude of the exposure and what effect(s) the exposure has are necessary to evaluate the consequences of the exposure (e.g., Berny 2007). Research in this area has focused on 3 lines of inquiry: (1) laboratory studies of toxicity in surrogate species, (2) correlating the levels of anticoagulant residues in tissues with specific toxicological endpoints, and (3) identifying effects other than direct mortality.

The toxicity of the anticoagulant compounds has been assessed in laboratory studies for a small number of species. These values are of limited utility for determining the effects of exposure on wildlife because susceptibility to the anticoagulants varies substantially between individuals and species (Erickson and Urban 2004). Such studies have also been criticized for being conducted under conditions that result in

unrealistic toxicity estimates (Vyas and Rattner 2012). The U.S. Fish and Wildlife Service has called for a more comprehensive approach to assessing the effects of pesticides on endangered species than is currently provided by the reliance on LD50 (the amount of rodenticide required to kill 50% of the test population) studies (Golden et al. 2011).

Concurrent with awareness that exposure to nontarget wildlife was occurring, early research on the effects of exposure focused on observing symptoms of toxicosis in laboratory studies to determine the effects of exposure, including mortality. Raptors and mammals were fed rodents or other animal tissues containing rodenticides under controlled conditions, but the dose was not measured (e.g., Evans and Ward 1967, Savarie et al. 1979, Mendenhall and Pank 1980). Symptoms documented in these studies and in the veterinary and medical literature include lethargy, anorexia, ataxia, anemia, lameness or immobility due to bleeding in the joints, and difficulty breathing (DuVall et al. 1989, Merola 2002, Spahr et al. 2007, Murray and Tseng 2008, Valchev et al. 2008). Work by Rattner et al. on captive American kestrels (*Falco sparverius*; Rattner et al. 2011) and eastern screech-owls (*Megascops asio*; Rattner et al. 2012, 2014*a*) examined the pharmacokinetics of first-generation anticoagulant exposure and developed toxicity reference values for a range of sublethal effects, including coagulopathy and hemorrhaging.

Exposure to anticoagulant rodenticides is confirmed by chemical analysis of the liver, other body tissues, blood, or the whole carcass for the specific anticoagulant compound (Vandenbroucke et al. 2008, Rattner et al. 2014*b*). Given the low concentrations of the rodenticides in the baits (25–50 ppm), residue concentrations detected in exposed individuals are at the low ppm level, or often in the parts per billion (ppb or μg/kg; Erickson and Urban 2004, Dowding et al. 2010).

Rodenticide levels in blood and tissues are determined by a multitude of factors, including the concentration in the bait (Kaukeinen 1982, Merson et al. 1984), the amount of bait consumed, the length of time the individual was exposed (single feeding or chronic), the time elapsed since the last exposure (Merson et al. 1984, Vandenbroucke et al. 2008), the half-life of the compound in the specific biological matrix (Vandenbroucke et al. 2008), and the rate at which an individual metabolizes and excretes the compound (Erickson and Urban 2004). Residue values cannot be used to determine the magnitude of the dose an individual has been exposed to since they vary widely even between individuals exposed to the same dose (Fisher 2006, Rattner et al. 2014*a*). Due to these factors, residue values from individuals exposed to the same rodenticide application will vary (Merson et al. 1984, Primus et al. 2001, Ebbert and Burek-Huntington 2010, Vyas et al. 2012).

Furthermore, the detection and quantitation of the anticoagulant rodenticides in biological matrices, such as blood and liver, may not be comparable between studies (Sánchez-Barbudo et al. 2012). There is considerable variation in the techniques used to recover rodenticides from sample matrices, as well as in the chemical analysis methods used to detect them (Goldade et al. 1998, Marek and Koskinen 2007, Vandenbroucke et al. 2008, Thomas et al. 2011). One study found that the chemical analysis method could underestimate the prevalence of SGARs in wildlife (Dowding et al. 2010).

The importance of conducting a thorough investigation to rule out other causes of mortality when investigating rodenticide poisonings has been stressed (Ebbert and Burek-Huntington 2010). To ensure that effects are conclusively attributable to rodenticide exposure, other toxic compounds (e.g., lead, mercury, selenium, organophosphates and other pesticides) and diseases (e.g., West Nile virus, avian influenza) should be tested for (Berny and Gaillet 2008, Kelly et al. 2014, Gabriel et al. 2015, Siers et al. 2016).

Studies attempting to correlate levels of anticoagulant exposure with effects have reported wide variability in lethal and sublethal effects among and within taxonomic groups, and there is no consistent trend in the findings among studies (Erickson and Urban 2004, Rattner et al. 2015, Murray 2017). For example, no correlations between residue level and mortality or symptoms of toxicosis were found in several studies on wild raptors environmentally exposed to rodenticides (Albert et al. 2010; Murray 2011, 2017), whereas laboratory studies with controlled doses of diphacinone and chlorophacinone in American kestrels did find correlations between mortality

or symptoms of toxicosis and liver residue levels (Rattner et al. 2011, 2015).

A probabilistic model using published data of liver SGAR concentrations from 270 individuals of 4 raptor species, which included the barn owl (*Tyto alba*), barred owl (*Strix varia*), great horned owl (*Bubo virginianus*), and red-tailed hawk (*Buteo jamaicensis*), estimated probabilities of toxicosis as a function of summed quantities of each anticoagulant liver residue value, for a total exposure per individual (Thomas et al. 2011). They found significant differences between species in the residue values at which symptoms occurred. When pooling the data from all 4 species (69 positive out of the 270 birds), 1 in 20 birds were predicted to show signs of toxicosis when liver concentrations were 0.02 mg/kg, and 1 in 5 birds were predicted to show signs of toxicosis when liver concentrations reached 0.08 mg/kg. Conversely, this means that 19 out of 20 birds were predicted to show no signs of toxicosis when liver concentrations were 0.02 mg/kg, and 4 out of 5 birds were predicted to show no signs of toxicosis when liver concentrations reached 0.08 mg/kg. Thomas et al. (2011) note that their results are applicable to the 3 owl species studied. While the probabilities of toxic effects estimated for specific residue values would be helpful in analyzing large datasets for these 3 owl species, they cannot be used to determine whether an individual owl with a given residue level succumbed to SGAR exposure, nor can they be used to conclude that individuals of other species were fatally exposed.

Because residue concentrations have not been consistently linked to thresholds for which adverse effects are expected to occur across different species, diagnoses using these data must be accompanied by full necropsy results (Berny 2007, Ebbert and Burek-Huntington 2010, Murray 2011). The lethal effects of exposure to anticoagulant rodenticides can often be confirmed by symptoms in necropsy. They generally include evidence of extensive hemorrhage (subcutaneous, intramuscular, pulmonary, visceral, or intracoelomic hemorrhage, pallor of internal organs) without concurrent evidence of corresponding severe trauma (such as fractures, wounds, or ocular injury; Murray 2011). In individuals with no obvious symptoms, histological examination can detect microhemorrhages (Rattner et al. 2011).

Sublethal effects of anticoagulant exposure other than coagulopathy and hemorrhaging are more difficult to document in wildlife. Sublethal effects observed in laboratory and clinical settings include anorexia, impaired mobility, and difficulty thermoregulating (Savarie et al. 1979, Swift 1998, Murray 2011, Vyas et al. 2014). Similar measures for confirmation of anticoagulant rodenticide exposure as the cause of mortality should be undertaken to confirm anticoagulant rodenticide exposure as the cause of a sublethal effect in sick individuals. The presence of an anticoagulant rodenticide in the blood or tissues is not conclusive, and other causes, such as pathogens, other pesticides, and anthropogenic contaminants should be tested for.

Few studies have examined physiological effects not directly related to impaired blood clotting. Data from a wild population of bobcats (*Lynx rufus*) were used to examine possible mechanisms by which anticoagulants could interfere with various aspects of immune system function (Serieys et al. 2018) and gene expression (Fraser et al. 2018). However, researchers were unable to produce immunosuppressant effects in domestic cats (*Felis catus*) in a laboratory study with brodifacoum (Kopanke et al. 2018). The inconsistent findings and conclusions from this group of studies highlight the need for significantly more research in this area.

Reproductive effects caused by exposure to anticoagulant rodenticides have primarily been documented as miscarriages and neonatal mortality in mammals (Mackintosh et al. 1988, Munday and Thompson 2003, Rady et al. 2013). Little information exists for birds. A study of barn owls (*T. a. javanica*) foraging in Malaysian oil palm plots treated with bromadiolone or chlorophacinone observed no effect on eggshell thickness (Salim et al. 2015), despite detectable levels of the compounds in the eggs. Although negative effects on brood size and the growth and survival of nestlings were documented, the rodent control itself could have reduced prey availability and explained the results (Salim et al. 2014, 2016). Another study that monitored owl nestlings in plots treated with brodifacoum or warfarin found reduced growth rates and also discussed prey availability as a possible cause (Naim et al. 2011).

Laboratory studies control for other factors

and can identify causal mechanisms, but reproductive effects from sublethal exposure to anticoagulant rodenticides are difficult to determine in laboratory studies. Mineau (2005) provided an extensive critique of why the standard laboratory reproductive toxicity tests with captive mallard (*Anas platyrhynchos*) and bobwhite (*Colinus virginianus*) were not likely to accurately assess the effects of pesticide exposure on wild birds. It is critically important and urgent that more research be directed toward understanding reproductive effects in the taxonomic groups with the highest exposure rates, such as raptors.

Conclusions

Research priorities

Addressing the following list of questions will result in better information on which to base regulatory decisions:

1. What proportion of a population is being sampled for rodenticide exposure and effects?
2. What proportions of exposed individuals are compromised?
3. How are primarily exposed nontarget species accessing rodenticide baits?
4. How are predators and scavengers being exposed when their diets do not include the target species?
5. How do we identify source locations (point of application)?
6. How do we apply toxicity results from small groups of taxonomically distant surrogate species in lab studies to wild populations of different species?
7. How should tissue residue values be interpreted?
8. What are the causal mechanisms linking exposure to sublethal and reproductive effects?

As with any stressor on a wildlife species, once identified, the next step is to determine the magnitude of its effect. Data quantifying the rate at which rodenticide exposure is occurring within populations and the proportion of exposed individuals affected, either directly or indirectly, are needed. Testing dead and moribund individuals is an inherently biased sampling design since it only examines a subset of a population while excluding the asymptomatic living portion. Studies should be designed to ensure that all individuals (live, moribund, and dead) within a population have an equal probability of being selected for rodenticide and other contaminant testing, their health and other potential causes of symptoms are assessed, and sample sizes are robust enough to support statistical analyses.

Because this is more challenging for rare and/or difficult to detect species, concurrent sampling of more common species that are taxonomically and ecologically similar within the same geographic area could be cautiously used to supplement data for the rarer and endangered species. A direct measure of the effect of the rodenticide exposure on survivorship and/or reproduction for each individual sampled must be included and compared against unexposed individuals within the population. The results can then be used to calculate the extent of the exposure and draw conclusions regarding the impact it is having on the population. Due to the high degree of variation in exposure and effects between individuals, species, and even between populations, as few extrapolations from other species should be used as possible, especially for important, sensitive, and rare species.

Information on exposure pathways, prevalence, and population effects will improve the ability of regulatory agencies to design measures that are effective in reducing risks to wildlife. While study designs for some of these questions will be challenging, I encourage researchers to engage in interdisciplinary collaborations that are necessary to resolve these complex issues.

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