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Anticoagulant Rodenticides and Wildlife: Introduction

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Chapter 1
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1 Setting the Scene

Rodents began to associate with humans at least from the early Neolithic era with the beginnings of systematic sequestering of food stores by humans (Cucchi and Vigne 2006; Reperant and Osterhaus 2014). About the year 541, the Justinian plague started amid the central granaries and crowded, unsanitary conditions of the later Roman cities. The resulting pandemic was the first documented example of the potentially devastating impact of commensal rodents on European society. The primary reservoir host and source of the plague was the black rat (*Rattus rattus*), which has widely thought to have disseminated from South-East Asia along land and marine trade routes (McCormick 2003). That plague spread through late Roman and early medieval Europe until the eighth century (McCormick 2003). About 600 years later, the Black Death was also vectored by *R. rattus*. Both pandemics were caused by *Yersinia pestis*, possibly infecting *R. rattus* via endemically infected burrowing rodents along the trade routes of Central Asia (Reperant and Osterhaus 2014); however, the strains were different between the pandemics, and the occurrences seemed to be independent (Wagner et al. 2014). *R. rattus* is considered to be the commensal reservoir of *Y. pestis* and fleas, the vectors between rats and humans, although in

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some Nordic countries human-to-human infections are thought also to have been important (Hufthammer and Walløe 2013). Additionally, recent assessments based on analysis of climate data suggest that *R.* rattus did not provide a reservoir and that overland routes were not the pathway, rather *Yersinia pestis* was repeatedly introduced into Europe from Asia via maritime routes (Schmid et al. 2015). Currently, the human plague is still affecting Asian and African countries, with thousands of annual casualties (Butler 2009). Rodents also carry a wide range of other bacteria as well as ecto- and endoparasites and viruses that pose a potential risk to human health (Battersby 2015).

Rodents also affect human food resources, both by consumption and fouling. In East Africa, average total crop losses due to rodents, are estimated to sometimes reach 80–100% (Makundi and Massawe 2011). In Tanzania, the average yield loss of maize is estimated to be 5–15%, potentially feeding 2.3 million people and costing approximately $40 million (Leirs 2003; 1998 United Nations data). In a study on crop damage due to rodents in Laos, it was shown that in certain regions losses may be up to 80% (Douangboupha et al. 2003). There are reports that in European and American countries, rodents also may affect agricultural practices by fouling and feeding on animal feed and crops, and potentially by acting as reservoirs for veterinary diseases (Stenseth et al. 2003). Losses to stored food from consumption, spillage, damage and contamination are of the order of 1–10% (Smith and Meyer 2015), but rodents also degrade crop yields and cause structural damage.

When introduced to islands, alien rodent species can spread rapidly, and may have devastating effects on local biota. For instance, over 100 of 123 major island groups in the world have been colonised by *Rattus* species, preying on local fauna and consuming vegetation, often impeding regeneration of seedlings (Amori and Clout 2003; Howald et al. 1999). Besides commensal rodents, also other (small) mammalian species have been introduced to islands (e.g., possums and mustelids in New Zealand; Alterio and Moller 2000; Eason et al. 2010). Introduction by humans is often non-intentional, but eradication is extremely difficult, usually associated with high costs and environmental impact.

In more recent time, additional problems have been associated with commensal rodents. For instance, rodents can destroy power and ICT cables, and damage insulation and other building materials (Shumake et al. 2000). This not only results in direct costs to the infrastructure, but may also impede work and result in dangerous situations when people are relying on sensitive life-saving equipment (e.g., in hospitals). Overall, rat-mediated losses in the US (excluding any human health costs) could amount to $19,000,000,000 per year (Pimentel et al. 2005), while estimates of equivalent costs for the UK are £200,000,000 per year (Battersby 2004).

The aforementioned socio/economic impacts of rodents clearly provide examples of the need to control commensal rodent populations. Historically, different methods have been applied, although we are unaware of any "scientific" descriptions of historic methods used. In ancient Egypt, Rome and India, cats (*Felis sp.*) and ferrets (*Mustela sp.*) have been associated with minimizing commensal rodent populations in agriculture, near granaries and food stores (Baldwin 1975; Faure and Kitchener 2009; Mark 2012). The painting "*Mérode Altarpiece"* by Robert Campin

(*circa* 1425–1428, Metropolitan Museum of Art, New York) shows a mousetrap, and although depiction of the mousetrap had a religious connotation and symbolism, it indicates the use of traps for rodent control in medieval times. The legend of the "Pied Piper of Hamelin" plays around 1284, and suggests that specific rat catchers were hired by people or cities to catch rats or to lure them away. In this period, primarily trapping was employed for rodent control although attempts were aimed at chemical control e.g. via herbs, to deter rodents. For instance John Gerard describes in the book "The Herball or Generall Historie of Plantes" (Gerard, 1597) how White Hellebore (*Veratrum album*) is effective in killing rodents: "The root giuen to drinke in the weight of two pence, taketh away the fits of agues, killeth mice and rats, being made vp with honey and floure or wheat" (sic). The roots of this plant species contain veratridine, a neurotoxic compound, a sodium ion channel agonist (Segura-Aguilara and Kostrzewa 2004).

The use of chemicals to control rodents (i.e. rodenticides) has been in practice for nearly a century, and is commonplace today. Most currently used rodenticides are anticoagulants, which prevent blood from clotting (Rattner et al. 2014). In the 1920s the discovery of the so called "Sweet clover disease", causing haemorrhage and even mortality in cattle due to poorly stored clover hay, lead to the detection of dicoumarol as the causing compound, and to the further development of the first-generation anticoagulant rodenticides (FGARs) based on related to the structure of warfarin (Link 1959).

Schein (1950) described the effectiveness of W.A.R.F. 42 (warfarin) as an anticoagulant rodenticide, and made the remark that it was highly effective on a short term, but that "environmental changes, such as reduction in the harborage or food supply, would give more profound and more permanent control, and is therefore to be preferred" . In another trial, warfarin was also considered to be very effective in controlling rats (Wayland and Gaines 1950). In that study, they used a very simple bait-station in order to prevent children from accessing and consuming poison, a first attempt to minimise non-target exposure. In 1952, the Association of Schools of Public Health published a recommendation on the use of warfarin, stating its effectiveness and the "relatively small hazard to man and useful animals compared to the hazard offered by most other effective rodenticides" (Anonymous 1952). None of those early reports mention issues with environmental risks. In the US, the use of rodenticides was regulated through the Federal Insecticide, Fungicide, and Rodenticide Act of 1947, in which environmental risks were not included (Ward 1965). At that time, the use of prolin, a warfarin based AR, was also promoted as an alternative for other methods of rodent control (e.g., arsenic trioxide, barium carbonate, endrin, fluoroacetimide 1081, strychnine, thallium sulfate, zinc phosphide) because those "methods have shown varying degrees of success, but with questionable safety to wildlife populations" (Libby and Abrams 1966). This suggests that the use of ARs was seen to be an environmentally friendly alternative. However, it was around that time that development of resistance of rodents to warfarin and diphacinone was first reported (Boyle 1960; Cuthbert 1963; Lund 1964). Although resistance to anticoagulants in rodents was widespread by the early 1970s, and likely to continue to spread, the UK Ministry of Agriculture, Fisheries and Food

stated "the appearance of strains of *R. norvegicus* and *Mus musculus* resistant to anticoagulants in Britain, Denmark, Holland and the US is a matter of concern, but there is no reason why other countries should not continue to develop and use anticoagulant rodenticides wherever they are suitable" (Bentley 1972). It was also stated that birds are generally resistant to anticoagulants, without further reference or data.

Despite the prevailing opinion that warfarin was both safe and effective, evidence began to accrue that some rodent populations were developing resistance to some FGARs (e.g., warfarin and diphacinone, Boyle 1960; Cuthbert 1963; Lund 1964). Possible mechanisms of resistance development include mutations at the receptor site with decreased binding affinity of the compounds (Lasseur et al. 2006; Meerburg et al. 2014; Pelz and Prescott 2015) or by modulation of metabolic activity (Ishizuka et al. 2008; Markussen et al. 2007).

Putatively in response to the development of resistance in some populations, more acutely toxic ARs were developed and promoted, so called second-generation anticoagulant rodenticides (SGARs). These "super warfarins" were largely effective in controlling rats that had developed warfarin resistance; a single feed delivered a toxic dose, thereby increasing the efficacy of control measures and reducing the likelihood of resistance development. However, in recent years, resistance towards some SGARs has been reported in rat populations (Buckle 2013; Meerburg et al. 2014). Besides the issue of resistance in decreasing the efficacy of the use of ARs, the potential risks of rodenticides to non-target rodents and secondary poisoning of predators is now recognized. Due to their persistence, SGARs in particular have been reported to accumulate in non-target rodent and bird species directly feeding on the baits (Brakes and Smith 2005; Hoare and Hare 2006; Tosh et al. 2011; Sánchez-Barbudo et al. 2012), even impacting local population densities (Brakes and Smith 2005). Secondary exposure and some poisoning of predators is also widely reported (e.g., Newton et al. 1990; Shore et al. 1996; Berny et al. 1997; Stone et al. 1999; Alterio and Moller 2000; Fournier-Chambrillon et al. 2004; Walker et al. 2008; Sage et al. 2010; Murray 2011; Thomas et al. 2011; Christensen et al. 2012; Sánchez-Barbudo et al. 2012; Elliott et al. 2013), as well as to scavengers (Howald et al. 1999).

2 Regulation of ARs: Environmental Risks Versus Societal Needs

Anticoagulant rodenticides are regulated under different frameworks. For instance, in Europe they are regulated either as plant protection product or as biocide, depending on their use. As a plant protection product, ARs are used in some countries to protect crops on fields. Biocidal use focuses on the control of rodents around buildings, properties, and industrial sites, and authorization is granted on the need to protect human health. Agricultural, rural and urban use of ARs

regulated under the Federal Insecticide, Fungicide and Rodenticide Act in the U.S. and through the Pest Control Products Act by Health Canada, with recent legislation limiting use of SGARs. This is because SGARs are considered to be PBT-compounds (Persistent, Bioaccumulative, Toxic), and generally fail the thresholds set for environmental risks. However, due to the societal need to control rodents, and the current lack of alternatives, the use of SGARs is still permitted in many situations under strict regulation of application. It has been shown that the way ARs are used can modulate the risks of secondary poisoning of predators (Shore et al. 2006), and the development and application of best practices may decrease the risks of exposure of non-target species to ARs (Tosh et al. 2011). This would shift the regulation of ARs from risk assessment to risk management, which would require clear insights into the spatio-temporal risks that ARs may pose to non-target species. Currently, alternative approaches and methods are being developed, in order to minimise risks. Effectiveness of such approaches in reducing environmental risks to non-targets and preventing the development of resistance, however, is yet to be established.

Recently we presented and discussed additional mitigation options available to stakeholders (industry, pesticide applicators, regulators and the public) on this issue (Elliott et al. 2016). Among the approaches discussed were the broader adoption of integrated pest management (IPM) programs by industry, and particularly, the U.S. EPA's advocacy for expanded IPM, which is also the direction the EU is promoting for Europe, including quantifying the effectiveness of the IPM measures in mitigating risks. Furthermore, industry's response with the "Go Green" programs of large retail establishments is considered a very interesting way forward. The UK has taken leadership by developing an industry led and sponsored AR stewardship scheme. It involves development of best practice for usage, education and outreach programs targeted at key user sectors, and monitoring of the outcomes of stewardship on user practice and on levels of non-target exposure and impacts (CRRU 2017). The state of California in the US has applied the approach of Ecofees, which are collected on sales of ARs and other vertebrate control chemicals (Timm et al. 2004; Hornbaker et al. 2012). The revenues of such Ecofees are used for research on the toxicity and environmental effects of current use rodenticides, and of new alternative products and safe use practices.

The development of alternative approaches for the control of commensal rodents requires research on mechanisms of exposure and effects in target and non-target species under real application conditions. Quantification of the risks associated with current use rodenticides is essential for assessing the effectiveness of the alternatives in mitigating risk. This book aims to provide a state-of-the-art overview of the scientific advancements in the assessment of exposure, effects and risks that currently used ARs may pose to non-target organisms in the environment, along with practical guidance for characterization of hazards. This will be discussed in relation to their efficacy, and the societal needs for rodent control, and discussion of risk mitigation and development of alternatives.

3 Background, Rationale and Outline for the Book

The idea for this book grew out of two scientific sessions on the impact of anticoagulant rodenticides on non-target wildlife, held at annual meetings of the Society of Environmental Toxicology and Chemistry (SETAC); the first from May 20 to 24, 2012 in Berlin, Germany, and the second from November 11 to 15, 2012 in Long Beach, California, U.S.A. Impetus partly came from the widespread interest in the topic evident by coverage of the Long Beach session in the international science media (e.g., Nature; Lovett 2012 and covered further in other e-media such as Scientific American News). Furthermore, based on a growing body of scientific evidence gathered over the last 20 years, it is now recognised that large-scale use of anticoagulants may pose a global risk to vertebrate wildlife as acknowledged by international agencies and conventions (e.g., United Nations Environmental Convention on Migratory Species 2014). We perceived, therefore, a need for a volume that focused on the environmental impact of ARs on non-target wildlife *per se*, rather than more general information on the chemistry and toxicology of these pesticides such as in another recent book (Buckle and Smith 2015). This book is the first attempt to comprehensively bring together all the available information on the environmental risks associated with rodent control using ARs. The overall aim of the book is to highlight current state of knowledge which will: (i) help shape and identify mitigation methods and effort in such a way as to reduce risk, and (ii) identify key gaps and uncertainties in our understanding and thereby point to major areas of future research and regulatory need.

The book begins with an overview of anticoagulant rodenticide use around the world (Chap. 2). In the following chapters, the focus is on controlled laboratory studies of anticoagulant toxicity (Chap. 3) and their pharmacokinetics in target and non-target species (Chap. 4). Chapter 5 presents diagnostics and clinical signs of AR toxicity. The perspective then widens to first assess the causes, scale and effects of primary exposure in non-target species (Chap. 6), followed by a chapter on secondary exposure of predators (Chap. 7). The spatial dimensions of how exposure and impacts vary are considered in detail in Chap. 8, while Chap. 9 addresses the key ecological factors affecting AR uptake. The important topic of resistance in target populations is examined in Chap. 10 and finally, regulatory aspects (Chap. 11), risk mitigation (Chap. 12) and development of alternative rodent control methods (Chap. 13) are analyzed. The final chapter describes projected needs for rodent control in the future, discusses the sustainability of AR use, and the need for alternative non-chemical or new chemical methods that are effective while minimizing non-target risks.

All chapters of this book describe the scientific background of the different topics addressed, but also reach out to a wider audience. Because of the diversity of topics, it was intended to make each chapter accessible on its own, so authors were encouraged to introduce the chapters in depth. The reader is of course encouraged to read the full book, but in this way it is also possible to focus on specific topics of interest. We hope that this facilitates the reader to use the book as a base of information for discussions and possibly even decisions, as it was intended for.

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