FACULTY OF VETERINARY MEDICINE
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EXPOSURE OF FLEMISH HEDGEHOGS TO ANTICOAGULANT RODENTICIDES

PART 1: RATIONALE

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1. Introduction

Anticoagulant rodenticides are widely used against pests. They disrupt blood coagulation resulting in internal haemorrhaging and death (Gommer et al., 2022). For a long time first generation products were used, but when target animals such as rats and mice showed resistance against these products, more potent products were developed, called the second generation products (SGAR's) (Baert et al., 2012). These SGAR's persist longer in animals after being ingested (Vandenbroucke et al., 2008). Non-target animals can also be exposed to anticoagulant rodenticides. In that case distinction is being made between primary and secondary intoxication. Primary intoxication is the direct uptake of anticoagulant rodenticides, while secondary intoxication is the uptake by eating prey containing levels of anticoagulant rodenticides. Secondary intoxication seems to have a bigger impact on wildlife than expected (Dowding et al., 2010; Guldemond et al., 2020). Most research focussed on secondary intoxication by the consumption of poisoned rodents in birds and mammals, but little research has been done around invertebrates as source of intoxication (Dowding et al., 2010). Although, it has been reported that snails can absorb anticoagulant rodenticides without experiencing any effects, hence forming a risk to snail eating species such as the Western European hedgehog (Dowding et al., 2010; Garcês and Pires, 2023; Guldemond et al., 2020).

2. Anticoagulant rodenticides

2.1 Products

Rodenticides are used in bait for rodent control (Watt et al., 2005). Many compounds are based on an anticoagulant mode of action. These anticoagulant rodenticides can be divided into two families: hydroxycoumarins and indandiones (Figure 1). The hydroxycoumarins are further divided into first and second generation compounds. The first generation contains coumatetralyl and warfarin, while second generation products include bromadiolone, brodifacoum, flocoumafen, difenacoum and difethialon (Buckle and Prescott, 1994; Lohr and Davis, 2018;

Pelfrène, 2010). The group of indandiones contain chlorophacinone, diphacinone and pindone, although this group is often included in the second generation compounds due to their similarity (Pelfrène, 2010).

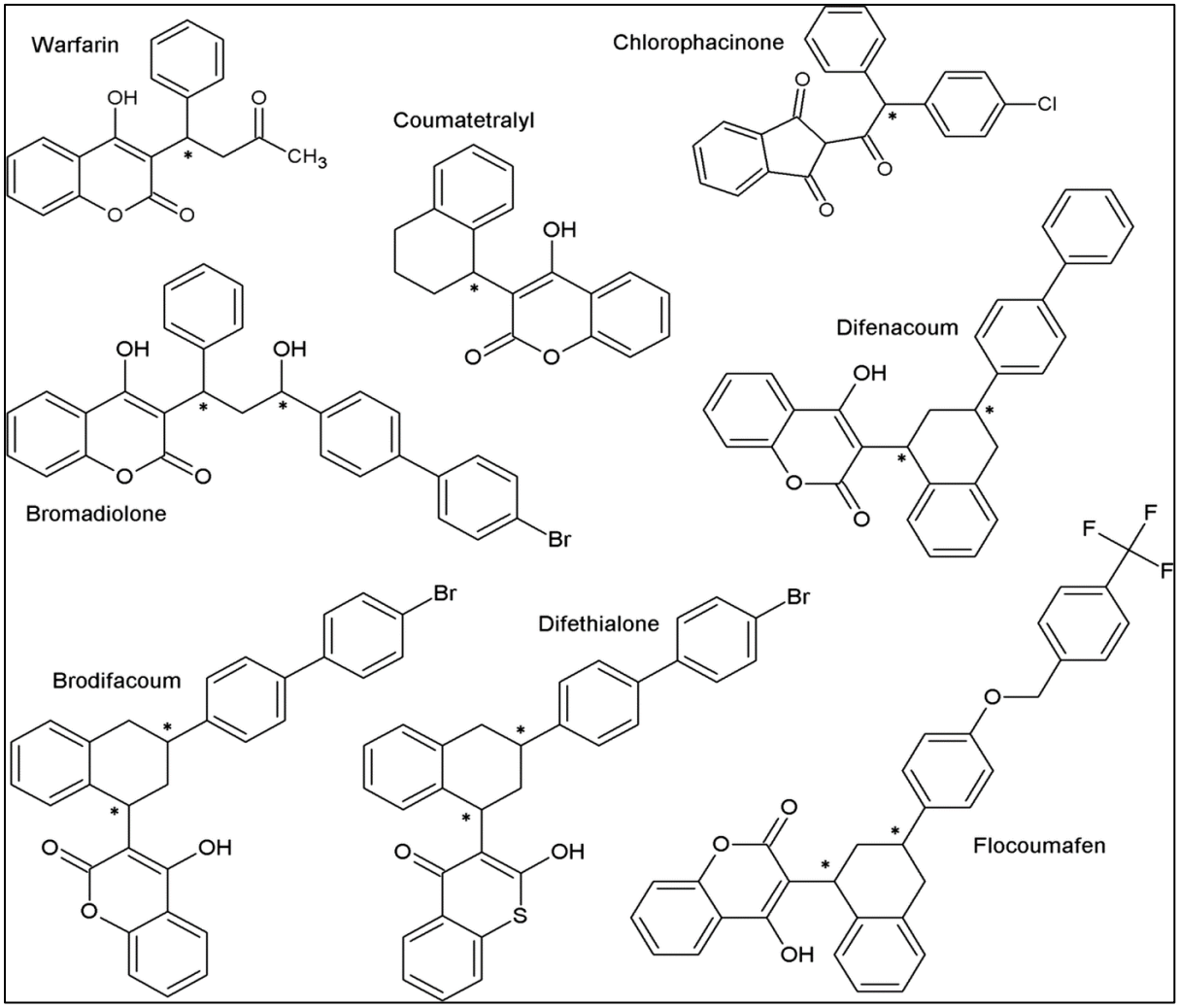

Figure 1: Chemical structures of anticoagulant rodenticides (Regnery et al., 2019)

The first generation anticoagulant rodenticides (FGARs) are less toxic than the second generation anticoagulant rodenticides (SGARs). This is due to SGARs being effective at a single dose, while the FGARs need multiple doses for their effectiveness (Lohr and Davis, 2018; Pelfrène, 2010; Vandenbroucke et al., 2008). There is also more resistance known for the FGARs, however resistance to SGARs is an upcoming and emerging problem in the rodent control sector (Baert et al., 2012; Buckle, 2013; Buckle and Prescott, 1994).

In human medicine coumarin derivates (acenocoumarol and fenprocoumon) are used to inhibit the blood clotting. These drugs are used for patients with atrial fibrillation, treatment of thrombo-embolism and are also used preventive in patients after a Transient Ischemic Attack, cerebrovascular accident or to prevent thrombo-embolism in orthopaedic procedure[1,2].

2.2 Pharmacokinetics

Because studies concerning the pharmacokinetics and pharmacodynamics of anticoagulant rodenticides in hedgehogs are lacking, this information will be based on what is known in other mammals, mostly mice and rats. Anticoagulant rodenticides are easily absorbed in the gastrointestinal tract after oral intake (Vandenbroucke et al., 2008). Once absorbed, different plasma levels for the first and second generation compounds are seen. The plasma elimination half-lives are shorter for the FGARs than for the SGARs. SGARs are more hydrophobic and have a higher affinity to the liver binding sites, therefore greater accumulation and persistence in the liver is seen (Pelfrène, 2010; Vandenbroucke et al., 2008). Anticoagulant rodenticides are metabolized by cytochrome P450 enzymes and are mostly hepatically cleared, resulting in elimination through feces (Popov Aleksandrov et al., 2024).

2.3 Pharmacodynamics

Anticoagulant rodenticides are antagonists of vitamin K, which is necessary for the synthesis of vitamin K-dependent clotting factors. These are clotting factor II, VII, IX and X (Popov Aleksandrov et al., 2024; Vandenbroucke et al., 2008). The normal pathway of activating the clotting factors is as follows; vitamin K is oxidised in the liver to vitamin K epoxide, which will lead to the activation of γ-glutamyl carboxylase that carboxylates glutamyl (Glu) to glutamate (Gla). Glutamate is needed to activate the clotting factors. Vitamin K epoxide reductase will further reduce the inactive vitamin K epoxide to active vitamin K again, so the

[1] Farmacotherapeutisch kompas van Nederlandse overheid. Vitamine K antagonisten. https://www.farmacotherapeutischkompas.nl/bladeren/groepsteksten/vitamine_k_antagonisten

[2] Belgisch centrum voor farmacotherapeutische informatie (BCFI), Anticoagulantia. https://www.bcfi.be/nl/chapters/3?frag=1974

pathway can start all over again (Fig. 2). However when exposed to anticoagulant rodenticides, the activation of vitamin K will no longer take place. This is because anticoagulant rodenticides inactivate the vitamin K epoxide reductase, decreasing the amount of active vitamin K, leading to depleting levels of active clotting factors (Gröber et al., 2014; Pelfrène, 2010; Popov Aleksandrov et al., 2024; Valverde et al., 2021). Due to the fact that the already formed clotting factors are not affected by this, it will take a few days before difference in coagulation is noticeable (Watt et al., 2005).

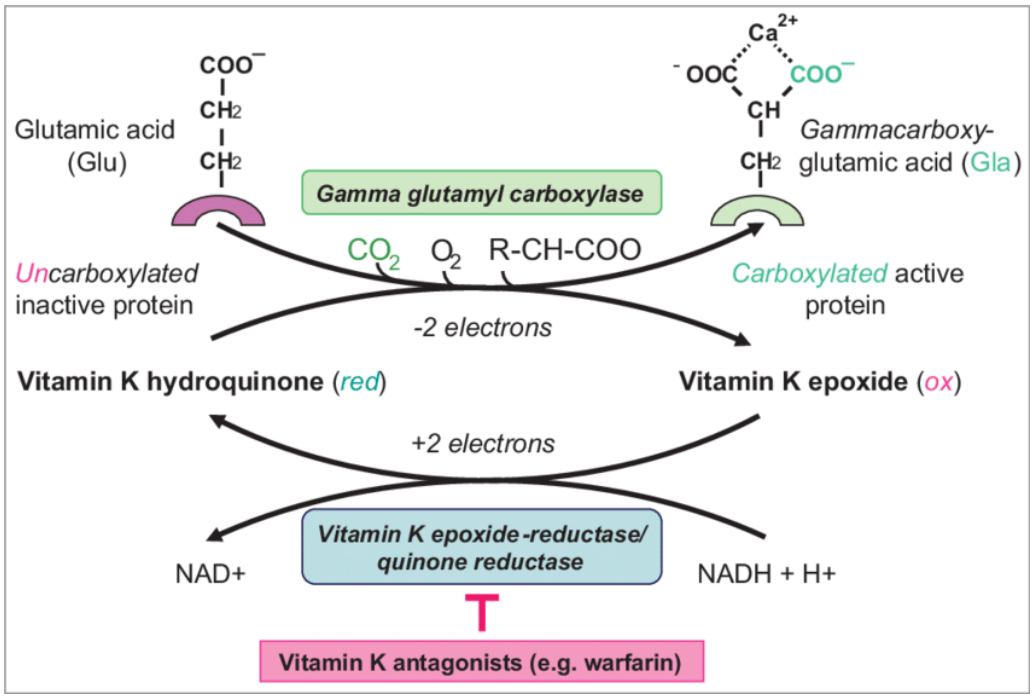

Figure 2: Vitamin K cycle (Gröber et al., 2014)

2.4 Hedgehog specific findings

"The ingestion of rodenticides can lead to severe health issues and even death in hedgehogs. Common symptoms of rodenticide poisoning in hedgehogs include internal bleeding, lethargy, weakness, loss of appetite, and in severe cases, seizures and death" (Garcês and Pires, 2023). There is one old study that found a difference in prothrombin (factor II) time depending on the season, this due to the fact that hedgehogs are hibernating animals. These authors reported that the prothrombin time is increased from September to December with a peak in November. This is important when interpreting the effects of anticoagulant rodenticides. They also found that

the effects of warfarine in hedgehogs were similar to that of guinea pigs. It resulted in a prolonged prothrombin time with no sex-specific difference (De Wit et al., 1985).

2.5 Legislation

Anticoagulant rodenticides are used to combat rodent plagues and in some cases to prevent. They are mainly used against house mice (*Mus musculus*), black rats (*Rattus rattus*) and brown rats (*Rattus norvegicus*). Because these products can have a major impact on the environment, humans and animals, the European Union provided legislation with respect to the use and sales of these product. Rodenticides fall under the regulation concerning biocides in group 14[3,4].

Biocides can only enter the market after being approved and registered by the authorities. If a product is allowed in different European member states, a parallel trade permit can be requested if the product is identical as in the state of origin. Manufacturers of biocides need to document safety information, used compounds, results of quality controls, batch identification, trades and transport. Importers, producers and sellers must keep invoices and tickets for 3 years.

These kind of products are also divided in two categories: a free circuit and a closed circuit. Free circuit products are below 0.003% concentration active substance and are allowed to be used by the public [5, 6]. This is ready-to-use bait placed in a secure baiting point. The maximum amount of bait in each package to buy is 100 g block bait or 50 g grain, pellet or paste bait for mice. For rats the maximum is 300 g block bait or 150 g grain, pellet or paste bait in each package. Bait is only allowed to be used in and around a building. Closed circuit products on the other hand are only allowed to be sold and used by professionals, or people that are registered. One can only become registered after following the right education provided by the local government. These professionals have more options in kind of bait, can buy up to

[3] VERORDENING (EU) Nr. 528/2012 VAN HET EUROPEES PARLEMENT EN DE RAAD van 22 mei 2012 betreffende het op de markt aanbieden en het gebruik van biociden https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32012R0528

[4] https://biocide.be/nl/biociden/productsoorten/rodenticiden by biocide.be

maximum 10kg of bait in a package and are allowed to use it in and around buildings, in open areas, dumping grounds and in/at sewers.

For all users, permanent baiting is not allowed except for targeting problem areas. When declared necessary, approved products must be used by a professional [5, 6].

Everyone that is registered needs to declare to the authority the amount of marketed biocides, every year before January 31st. The Belgium authority collects this data and publishes it. In Figure 3, the data collected between 2018 until 2022 are shown. The left graphs show the number of products on the market and number of active substances. It is however not clear how many of these rodenticides are anticoagulant rodenticides. On 7th of May 2024, 10 active substances were used, of which 6 were anticoagulant rodenticides. In total 99 products were being sold of which 88 products were anticoagulant rodenticides according to biocide.be. The right graphs show the amount of products sold and substance quantity in ton. Again it is not clear what the exact amount of anticoagulant rodenticides is, due to the data containing all rodenticides. But it gives a clear view that there is a lot of usage in Belgium of rodenticides.

Figure 3: Number of registered (left) and sold (right) rodenticides in Belgium[7]

The overuse of biocides and the impact usage can have on our health and environment, is the reason why a federal reduction program for biocides is set up and used since October 2023.

[5] KONINKLIJK BESLUIT van 4 april 2019 betreffende het op de markt brengen en gebruiken van biociden https://www.ejustice.just.fgov.be/mopdf/2019/04/23_1.pdf#Page31

[6] https://biocide.be/nl/biociden/productsoorten/rodenticiden by biocide.be

[7] https://apps.health.belgium.be/files-dwh-ext/files/gau/index.html by biocide.be

This program will focus on educating the public and professionals about safe usage and consequences abuse can have, improving the knowledge of users, reducing the amount and products that are not allowed on the market, reducing resistance, follow-up of seller to user especially of dangerous products and researching the exposure and impact of biocides on our health. This program will be evaluated every 2.5 years [8,9].

3. Hedgehogs

3.1 Distribution and habitat

The western European hedgehog (*Erinaceus europaeus*) is widely spread through Western and Northern Europe (Figure 4). Males tend to have a greater ranging behaviour compared to females (Dowding et al., 2010). Hedgehogs seem to be adjusted to a variety of habitats (Huijser, 1999). Their natural habitat is rural areas such as woodlands and grasslands. But it seems there has been a big preference shift to urban areas such as green gardens and parks (Garcês and Pires, 2023; Hubert et al., 2011; Rasmussen et al., 2019). However in these urban areas the hedgehog faces new dangers such as traffic, rodenticides, domestic animals, human disturbance, drowning in ponds, lawn mowers, being stuck in nets and trash (Bright and Holloway, 2009; Gazzard et al., 2022; Korslund et al., 2024; Reeve et al., 2024). It has been suggested this shift is due to the presence of predators and intensive agriculture in rural areas (Huijser, 1999; Korslund et al., 2024). But there is a study that investigated which habitat the hedgehog preferred based on their density in various habitats. This showed that they prefer urban areas with vegetation and small scale agriculture landscape with hedgerows and woodland fragments, but that for example in the Netherlands between 1900 and 1990 there was a decrease in length of hedgerows and rows of trees by 50% and a 80% increase in agriculture

[8] Koninklijk besluit van 26 oktober 2023 tot vaststelling van het federaal reductieplan biociden https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2023102612&table_name=wet

[9] Reductieplan biocide.be van de vlaamse overheid https://biocide.be/nl/veiligheid-en-milieu/reductieplan#:~:text=ge%C3%ABvalueerd%20kan%20worden.-,Structuur%20van%20het%20reductieplan,voor%20specifieke%20gebruiken%20van%20biociden.

field size (Dijkstra et al., 1997; Huijser, 1999). Hence, this results in a decline in preferred habitat.

Another reason found for decline in habitat is fragmentation. Fragmentation can be caused by barriers. These barriers can be uncrossable by the hedgehog such as walls, fences and train tracks, but they have also seen that hedgehogs tend to avoid roads, especially when they are wider. Fragmentation can result in an isolation of the population (Moore et al., 2020; Taucher et al., 2020).

Figure 4: distribution of the west European hedgehog [10]

[10] IUCN (International Union for Conservation of Nature) 2008. Erinaceus europaeus. The IUCN Red List of Threatened Species. Version 2023-1.
https://www.iucnredlist.org/species/29650/2791303#geographic-range

3.2 Diet

The Western European hedgehog is an insectivore, this means his main diet contains a variety of insects, but they will also feed themselves on carrion, earthworms, eggs, slugs, snails and small amounts of plant material (Gimmel et al., 2021). However in urban areas humans will feed the hedgehogs with a variety of products such as pet food or commercial hedgehog food (Garcês and Pires, 2023; Gimmel et al., 2021).

3.3 Population problems

The Western European hedgehog currently has the status of "not endangered" on the red list of Flemish mammals (Maes et al., 2014). However this list is dated from 2014 and the Institute for Nature- and Forest Research (Instituut voor Natuur- en Bosonderzoek or INBO) states that there is a decline in the hedgehog population[11]. In 2019, Timo Van der Veken, a student of Ghent University used 'waarnemingen.be' as an monitoring tool, and this data suggest that the hedgehog population was declining by around 50% between 2008 to 2017. Even a decline in distribution has been seen (Van der Veken et al., 2019; Van der Veken and Hoffmann, 2020). In other countries there have also been indications that the hedgehog population has been declining (Rasmussen et al., 2023; Reeve et al., 2024; Taucher et al., 2020). In 2020 the population status of the hedgehog in the United Kingdom even has been changed to vulnerable (Mathews and Harrower, 2020).

As mentioned earlier, using urban areas as habitat means the hedgehog faces many new dangers that may put pressure on the population (Taucher et al., 2020). Roads are a big problem. Every year many hedgehogs get run over. The Flemish government started a project called 'Dieren onder de wielen' to map the number of animals killed by traffic in Belgium. The last reports from between 01/03/2017 and 30/11/2020 showed the hedgehog was number one most reported

[11] Instituut voor natuur- en bosonderzoek; De achteruitgang van de egel in Vlaanderen – een stekelige kwestie. 21/03/2024 https://www.vlaanderen.be/inbo/nieuws/de-achteruitgang-van-de-egel-in-vlaanderen-een-stekelige-kwestie/

traffic victim with 4,707 reported deaths. Seasonal variation in traffic deaths is also seen in hedgehogs. December to March has the lowest traffic victim count due to the hedgehog hibernating in this period. From May reproduction season starts resulting in an increase in traffic victims. In June and July a peak of mostly male hedgehogs is seen due to the fact they are trying to find a mating partner. In autumn younglings become independent resulting in a small peak (Jacobs et al., 2021). This all suggests that roads can have a major impact on the hedgehog population.

Since around 2020 hedgehogs are brought to wildlife centres with wounds and ulcerative lesions on their head and limbs. A study in Belgium and Germany found that most of these patients had a positive culture with *Corynebacterium ulcerans* (Fig. 5). This is a zoonotic gram-positive bacterium that if it has a ToxE gene, can produce toxins that cause diphtheria. Besides the skin lesions, it can also affect the lungs and other organs. It has been suspected to be an opportunistic pathogen, although no primary cause of disease has been found. The reason for this is that there was a higher incidence seen in male hedgehogs, suggesting its due to male-specific behaviour such as biting in mating season due to the occurrence of their lesions. Mostly skin that is not protected by their spines, is affected (Berger et al., 2019; Martel et al., 2021; Terriere et al., 2022). However in the Netherlands the University of Utrecht DWHC (Dutch wildlife health centre) is still in doubt *C. ulcerans* is the cause of these skin lesions. They found only one case of *C. ulcerans* in a group of 24 hedgehogs with skin lesions, and it was non toxin producing (DWHC, 2021).

Figure 5: Leasions of Corynebacterium ulcerans (right: Berger et al., 2019; left: Martel et al., 2021)

Another finding is that hedgehogs seem to be exposed to anticoagulant rodenticides. Multiple studies in different countries found anticoagulant rodenticides in liver samples (Williams et al., 2023), sometimes even at the same ratio that specialist predators of small animals are exposed to (Dowding et al., 2010). Male hedgehogs seem to be more exposed to anticoagulant rodenticides, assumably due to having a higher ranging behaviour compared to females(Dowding et al., 2010). Although lethal poisoning is rare in hedgehogs, studies in other species indicate that exposure at non lethal dosage can effect a population (Dowding et al., 2010; Guldemond et al., 2020). So this may contribute to some problems the hedgehog population is facing today (Garcês and Pires, 2023).

4. Secondary intoxication in small mammals

Anticoagulant rodenticides are toxic to all vertebrates and have been detected in livers of multiple wildlife species, therefore more and more research is being done to determine the pathway of exposure and effects it can have on populations (Koivisto et al., 2010). Exposure can be through direct uptake of bait. Non-targeted animals can be directly exposed to bait due to intentional poisoning, misuse of bait, non targeted animals being able to enter bait boxes and rodents dragging bait out of bait boxes (Gommer et al., 2022; Guldemond et al., 2020; Koivisto et al., 2010; Valverde et al., 2021). Indirect poisoning, also known as secondary intoxication happens when animals, faces or carcasses exposed to anticoagulant rodenticides, are consumed by other animals (Dowding et al., 2010; Koivisto et al., 2010). When ingested, anticoagulant rodenticides can persist for long periods of time in the liver of animals after sub lethal exposure. Anticoagulant rodenticides seem to persist in the environment, depending on the soil type and seasons. Bromadiolone elimination half-life seems to range from 1.8 to 53 days (Sage et al., 2007). Eason et al. (2002) reported liver retention in rats and some other species to be 0.5-1 month for warfarin, 3-6 months for coumatetralyl and diphacinone and 6-12 months for difenacoum, bromadiolone, flocoumafen, brodifacoum and difethialone, with brodifacoum

having the longest half-life. Invertebrates may also be a source, as it seems snails/slugs do enter the bait boxes, consume bait without clinical effects (Alomar et al., 2018; Gommer et al., 2022; Guldemond et al., 2020; Koivisto et al., 2010). Anticoagulant rodenticides can be retained in the body of invertebrates for weeks or longer (Dowding et al., 2010). It has been assumed that uptake of contaminated invertebrates by hedgehogs, is the main source of exposure (Alomar et al., 2018). However more research is needed to determine if this is correct.

Exposure of lethal dosage will result in haemorrhaging and death (Hernandez-Moreno et al., 2013; Koivisto et al., 2010). However less is known about the effects of sub-lethal dosage (Shore et al., 2003). In humans, sometimes warfarin treatment gave as side-effect skin necrosis (Chan et al., 2002). Fraser et al. (2018) found a correlation between anticoagulant rodenticide exposure and the intensity of mange infection in bobcats (*Lynx rufus*). Fraser reported that in anticoagulant rodenticide positive bobcats, the expression of genes involved in an allergic immune response were supressed, along with reduced monocytes and B-lymfocytes, meaning a compromised immune response. Further, downregulation of genes necessary in epithelial formation and maintenance was seen, suggesting anticoagulant rodenticides can have an effect on skin and immunity (Fraser et al., 2018; Koivisto et al., 2010). A study in red foxes (*Vulpes vulpes*) observed higher median concentrations of anticoagulant rodenticides in animals killed by infectious disease, than in animals killed by trauma, suggesting a corelation between infection and anticoagulant rodenticide exposure (Carrera et al., 2024). However a study done in cats (*Felis catus*) exposed to chronic low levels of brodifacoum found only a decrease in IL-4 and IL-6, that might influence the proliferation of B-cells and IgE isotype switching (Kopanke et al., 2018). A study in voles (*Arvicola terrestris sherman*) suggests an interaction between chlorophacinone treatment and *Francisella tularensis*, due to the fact that death voles with this infection showed lower chlorophacinone levels than non infected voles (Vidal et al., 2009). In

conclusion, there might be a possibility of interaction between anticoagulant rodenticide exposure and infectious diseases, immune system and/or wound healing.

5. Research hypotheses

This literature study shows little research has been done about the exposure and effects of anticoagulant rodenticides in hedgehogs, thus more research needs to be done. Therefore multiple hypotheses are of interest. First of all, 'are Flemish hedgehogs exposed to anticoagulant rodenticides?'. As discussed earlier, there are indications of dropping population numbers and the increase of *C. ulcerans* infections in hedgehogs. As there might be a correlation between anticoagulant rodenticides exposure and the findings, researching if Flemish hedgehogs are exposed, could be really interesting. Since anticoagulant rodenticides accumulate in the liver, liver samples should be tested. In terms of exposure, exposed slugs and snails might be a source of secondary poisoning for hedgehogs, leading to the second hypothesis 'are slugs a source of anticoagulant rodenticides?'. As it seems, the impact of sub-lethal chronic exposure of anticoagulant rodenticides is still unknown. Therefore researching 'what is the influence of anticoagulant rodenticides on the immune system and recovery?' could really benefit multiple wildlife species. For this hypothesis, African hedgehogs (*Atelerix albiventris*) will be exposed to a low sub lethal dosage of anticoagulant rodenticides and will be vaccinated afterwards, to see if there is a difference in antibody production between the exposed and control group. In addition, small biopsies will be taken to see if there is a difference in skin healing between the exposed group and the control group.

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