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Review paper

Anticoagulant rodenticides in game meat: a risk to human health

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ABSTRACT

Although rodents are the largest taxonomic groups of all mammals, only about 5% of them are considered pests. Rodent pest control is used to control commensal rodents such as Norway rats (*Rattus norvegicus*), roof rats (*Rattus rattus*), and house mice (*Mus musculus*). Methods used for rodent pest control are: trapping, poisons, habitat management, fertility control, barriers, repellents (acoustic and olfactory), behavioural mechanisms, predators or parasites, control of ectoparasites or pathogens, damage prevention and forecasting, etc. One of the most widespread methods in the world is the application of poisons. The most common are anticoagulant rodenticides, which are divided into first-generation anticoagulant rodenticides and second-generation anticoagulant rodenticides. Considering that anticoagulant rodenticides are indiscriminate and can affect all vertebrates, there is a high risk of unintentional poisoning of non-target wildlife or domesticated animals. Therefore, there is growing concern about the detection of second-generation anticoagulant residues in a large number of animal species. Their accumulation in the environment can cause anticoagulants to transfer along the food chain, causing potentially serious health consequences for wildlife and humans.

1. Introduction

Rodents are one of the largest taxonomic groups of all mammals. Of the 5419 mammalian species, approximately 42%, or 2,277 species, are rodents. They are found on all continents except Antarctica (*Wilson and Reeder*, 2005; *Yu et al.*, 2020). Rodents are highly adaptable animals, with a wide distribution and diverse impacts on the economy, environment, agriculture, food security and safety, biodiversity, public health, etc. (*Capizzi et al.*, 2014; *Jacoblinnert et al.*, 2022). Despite their great species diversity and widespread distribution around the world, only about 5% of rodents are considered pests (*Witmer*, 2018). Rodent pest control is used to control commensal rodents' population, such as Norway rats (*Rattus norvegicus*), roof rats (*Rattus rattus*), and house mice (*Mus musculus*), which represent not only economically important pests, but also a serious public health problem (*Quinn et al.*, 2019). It is estimated that 5% of food produced in the world is eaten or damaged by rodents (*Jurišić et al.*, 2022). In addition, rodents can transmit more than 40 zoonotic pathogens to humans in a variety of ways, both directly and indirectly (*Buckle and Smith*, 2015). The house mouse and roof rat are listed among the 100 World's Worst Invasive Alien Species by the IUCN/ISSG (Invasive Species Specialist Group).

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2. Rodent pest control

Methods used for rodent pest control are: trapping, poisons, habitat management, fertility control, barriers, repellents (acoustic and olfactory), behavioural mechanisms, predators or parasites, control of ectoparasites or pathogens, damage prevention and forecasting, etc. (*Capizzi et al.*, 2014). One of the most widely applied methods for pest control is the use of poisons. Anticoagulant rodenticides are the most commonly used of all poisons, and as of 2017, accounted for more than 95% of rodenticides approved as biocides in the European Union (*Capizzi et al.*, 2014; *ECHA*, 2017; *Kotthoff et al.*, 2019).

Many different biocidal products are registered as rodenticides worldwide and classified into three main classes: acute, subacute, and chronic rodenticides. The acute and subacute poisons include compounds such as arsenic, strychnine, zinc phosphide, sodium monofluoroacetate, alphachloralose, thallium sulphate, calciferols, bromethalin and others (*Buckle and Smith*, 2015). Of these, zinc phosphide is still allowed for use in many countries, including in Serbia.

Anticoagulant rodenticides are the most effective and most commonly used biocidal products (*Regnery et al.*, 2019). According to *Capizzi et al.* (2014), anticoagulants were used in 61% of cases of pest control. Anticoagulant rodenticides are divided into first-generation anticoagulant rodenticides (FGAR) (i. e. pindone, diphacinone, chlorophacinone, warfarin, and coumatetralyl) and second-generation anticoagulant rodenticides (SGAR) (i. e. difethialone, brodifacoum, bromadiolone, flocoumafen, and difenacoum). FGARs show a lethal effect on consecutive multiple oral intakes, while SGARs are more toxic, and single feeding is often sufficient for a lethal dose (*Fisher et al.*, 2019).

Anticoagulant rodenticides inhibit the production of vitamin K by blocking the activity of vitamin K epoxide reductase and subsequently clotting factors (II, VII, IX, and X) involved in the blood coagulation process. Therefore, poisoned animals die from internal haemorrhage within 3 to 7 days (*Buckle and Smith*, 2015; *Damin-Pernik et al.*, 2016).

3. Anticoagulant rodenticides and impact on non-target animals and wild game

Considering that anticoagulant rodenticides are indiscriminate and can affect all vertebrates, there is a high risk of unintentional poisoning of non-target wildlife or domesticated animals (*Regnery et al.,* 2019).

Exposure of wildlife (non-target animals) to anticoagulant rodenticides occurs via three pathways: 1) direct ingestion of rodenticide bait (primary exposure), which is common in herbivores and omnivores because most baits are cereal-based, 2) direct consumption of unabsorbed rodenticides from the digestive tract of prey (secondary exposure), and 3) indirect exposure typically occurs when an animal consumes poisoned prey that carries residual concentrations of anticoagulant (tertiary exposure) (*Morzillo and Mertig*, 2011, *Regnery et al.,* 2019).

All SGARs, due to their high risk to human health and the environment, have been identified as being either persistent, bioaccumulative, and toxic or very persistent and very toxic (*Kotthoff et al.*, 2019), hence have a higher risk of poisoning non-target animals in comparison to the FGARs (*Fisher et al.*, 2019).

Widespread use of anticoagulant rodenticides can lead to the accumulation of anticoagulants in the environment, and consequently, poisoning and accumulation of anticoagulant rodenticide residues in non-target terrestrial and aquatic species. Furthermore, the accumulation of anticoagulants in the environment can lead to their transfer along the food chain, with potentially serious health consequences for wildlife and humans (*Regnery et al.*, 2019). Therefore, there is growing concern about the detection of second-generation anticoagulant residues in different tissues of a large number of animal species, e.g., barn owls (*Geduhn et al.*, 2016), foxes (*Geduhn et al.*, 2015), hedgehogs (*Dowding et al.*, 2010) and snails (*Alomar et al.*, 2018), including game, e.g., black bear, wild pigs (*McMillin et al.*, 2018) and white-tailed deer (*Stone et al.*, 1999). Considering the abovementioned issues, these residues pose a potential danger to human health.

SGARs have liver half-lives of >80 to 350 days and are typically used only for rodent pest control (*Erickson and Urban*, 2004, *McMillin et al.*, 2018). SGARs contain two asymmetric carbons in their chemical structure and each is a mixture of four stereoisomers assembled into two pairs of diastereoisomers (*cis*-diastereoisomers or *trans*-diastereoisomers), each pair containing two (1R,3R) (1S,3S)-isomers and (1R,3S) (1S,3R)-isomers in different proportions, with different pharmacokinetic properties and biological activities. There is always one diastereoisomeric form with a shorter half-life than the other one, so the risk of secondary poisoning in predators can differ between isomers (*Lefebvre et al.*, 2017; *Alabau et al.*, 2020).

Wild animals can become exposed to rodenticides in urban, suburban and agricultural areas where the use of rodenticides against commensal rodents is continuous, or in farmland areas where the use of rodenticides is periodically intensive (*López-Perea et al*., 2018). However, intensive use of rodenticides in the environment can lead to long-term chronic accumulation of SGAR in predators or can cause fatal poisonings in many different species of non-target animals with secondary poisoning in predators (*Olea et al*., 2009).

Game animals are also at risk of exposure to SGARs, especially omnivorous species, such as wild boar (*Sus scrofa*), by the direct ingestion of rodenticide baits or by the consumption of carcasses of animals poisoned by rodenticides (*Alabau et al*., 2020).

Alabau et al. (2020) indicated a high prevalence of rodenticides liver and muscle of wild boars in urban areas (60.8%), suburban areas (40%) and rural areas (7.7%). These results showed a positive relationship between the presence of SGAR residues in wildlife and human population density, most likely because of the intensive use of rodenticides for rodent pest control in urban areas, consequently leading to long-term chronic accumulation of rodenticides in wildlife. This indicates a potential risk to game meat consumers. Namely, although rodenticide doses are low, wild game in urban areas could have much higher concentrations of rodenticides in meat and other organs, which would increase the risk to human health (*Alabau et al*., 2020).

4. Anticoagulant rodenticides in wild game edible tissues and risk to human health

The use of anticoagulants. primarily warfarin and diphacinone, as antithrombotic therapy in humans is well known. However, problems regarding involuntary exposure can occur when anticoagulants enter the food chain, primarily through foods of animal origin. One example is the presence of anticoagulant residues in game meat, which is a potential hazard to human health, primarily in regions where game meat is often consumed *(López-Perea et al*., 2018).

Game meat has exceptional nutritional value, low fat content, and good digestibility. The skin of game animals is lighter and thinner than that of domestic animals, resulting in a higher meat yield in the total carcass weight. For example, the amount of meat in roe deer, European deer, and mouflon ranges from 55 to 70%. The percentage of fat in meat differs between the different types of game: from 3.85% in deer thigh meat to 0.98% in pheasant breast meat (*Zakula*, 1976).

Since game meat is not widely available to the public, it does not occupy a significant place in the diet, except for hunters. According to data from 2021, there are over 87,500 hunters in Serbia (*Anon*, 2022). The average game meat consumption per capita in Serbia is 0.14 kg, whereas per hunter, it is 17.22 kg. This consumption is much lower compared to other European countries, where Austria has the highest average game meat consumption per capita (1.21 kg), while Hungary has the highest consumption per hunter (146.86 kg).

Table 1 shows the ten-year average of planned and executed hunting of the most important big game in Serbia (*Anon*, 2022). Based on this data, it has been estimated that the production of game meat per 100 ha in Serbia is similar to in Croatia, averaging around 15.65 kg. However, this is more than seven times less than the production of game meat in Austria, over five times less than in the Czech Republic, Hungary, and Germany, and more than half of that in Slovakia (*Anon*, 2021).

Table 1. The number of animals of the four big-game species in Serbia (from 2011–2021) according the planned and executed game shooting (Anon, 2022)

Year	European deer	European fallow deer	Roe deer	Wild boar	European deer	European fallow deer	Roe deer	Wild boar
	Planned game shooting				Executed game shooting			
2011	823	169	12824	8046	653	114	8039	4962
2013	1122	351	14017	10365	870	182	8529	6475
2015	1366	309	15683	11023	1035	99	9279	7775
2017	1243	168	16962	13939	856	85	10544	11179
2019	1145	293	17689	15942	813	229	10484	12919
2021	1429	246	19503	20560	984	188	11454	15228

In the study by *Eason et al.* (1999, 2001), the accumulation of brodifacoum in various tissues of different wild game is reported. Namely, the brodifacoum concentration in wild boar was in the range from 0.007 to 1.7 mg/kg in the liver, and from 0.01 to 0.07 mg/kg in muscle; in red deer (*Cervus elaphus*) the concentration was up to 0.02 mg/kg in muscle and 0.03 mg/kg in liver; and in goat (*Capra hircus*) the brodifacoum concentration was up to 0.01 mg/kg in liver. *McMillin et al.* (2018) demonstrated that in the black bear (*Ursus americanus*) liver, the concentration of residual anticoagulants was 8.7 mg/kg. The Authors indicated that at such a high concentration of rodenticide, a 60 kg human would need to consume 2.68 kg of liver to reach mammalian LD_{50} values (0.39 mg/kg body weight for rats) of brodifacoum.

Research conducted by *Pitt et al.* (2011) found that cooking has an impact on diphacinone residues concentration in meat, thereby increasing its potential hazard to human health. In that study, the concentration of diphacinone increased in all tissues after cooking, which could indicate that water loss during heating tended to concentrate diphacinone in tissues.

Eisemann and Swift (2006) indicated the hazards of maximum concentrations of diphacinone residues in pig muscle (0.25 mg/kg), pig liver (3.07 mg/kg) and game liver (0.56 mg/kg). They reported that a 55 kg person would have to eat 28.49 kg of pork meat, 2.33 kg of pork liver or 12.77 kg of game liver to reach a dose of diphacinone equivalent to that affecting blood clotting in rats, while pregnant women of the same weight (55 kg) would have to ingest 5.50 kg, 0.45 kg or 2.46 kg, respectively, for the amount of diphacinone equivalent to the dose that has been shown to cause foetal reabsorption in rats.

Although it seems unlikely that all this could happen in one day, the risk is reflected in the facts that some SGARs are highly accumulative and that repeated exposure increases the risk of adverse effects of anticoagulants, and people who use antithrombotic therapy should be especially careful (*López-Perea et al.*, 2018).

5. Conclusion

Anticoagulant rodenticides have been used for more than half a century and today are the most commonly used biocides for rodent pest control. Widespread use of these poisons can lead to poisoning and accumulation of anticoagulant rodenticide residues in the environment and wild animals. Anticoagulant rodenticides can occur in the environment due to several pathways: during the production of the active substance, the formulation of the biocidal product, the application of baits, and the disposal of baits. Entry of rodenticides into the food chain is a big risk, which can potentially lead to serious problems for human health. Although anticoagulant residues were found only in low levels in wild game tissues, these chemicals can potentially affect human health. Given the seriousness of the problem likely in the future, more research is needed to properly deal with anticoagulant residues in game meat.

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References

Alabau, E., Mentaberre, G., Camarero, P. R., Castillo-Contreras, R., Sánchez-Barbudo, I. S., Conejero, C., Fernández-Bocharán, M. S., López-Olvera, J. R. & Mateo, R. (2020). Accumulation of diastereomers of anticoagulant rodenticides in wild boar from suburban areas: Implications for human consumers. *Science of the Total Environment*, 738, 139828, https://doi.org/10.1016/j.scitotenv.2020.139828

Alomar, H., Chabert, A., Coeurdassier, M., Vey, D. & Berny, P. (2018). Accumulation of anticoagulant rodenticides (chlorophacinone, bromadiolone and brodifacoum) in a non-target invertebrate, the slug, *Deroceras reticulatum*. *Science of the Total Environment*, 610, 576–582, https://doi.org/10.1016/j.scitotenv.2017.08.117

Anon, (2021), https://www.lorist.co.rs/znacaj-mesa-divljaci-u-ishrani-ljudi/ (Assessed on July 31, 2023).

Anon, (2022). Statistical Yearbook of the Republic of Serbia, Statistical Office of the Republic of Serbia, Belgrade, https://data.stat.gov.rs/Home/Result/13040601?languageCode=sr-Latn&displayMode=table&guid=f64a952d-6d44-4cd1-9787-775c1543c09a

Buckle, A. & Smith, R. (2015). Rodent pests and their control (2nd ed.). CAB International.

Capizzi, D., Bertolino, S. & Mortelliti, A. (2014). Rating the rat: global patterns and research priorities in impacts and management of rodent pests. *Mammal Review*, 44(2), 148–162, https://doi.org/10.1111/mam.12019

Damin-Pernik, M., Espana, B., Lefebvre, S., Fourel, I., Caruel, H., Benoit, E. & Lattard, V. (2016). Management of rodent populations by anticoagulant rodenticides: toward third-generation anticoagulant rodenticides. *Drug Metabolism and Disposition*, 45(2), 160–165, https://doi.org/10.1124/dmd.116.073791

Dowding, C. V., Shore, R. F., Worgan, A., Baker, P. J. & Harris, S. (2010). Accumulation of anticoagulant rodenticides in a non-target insectivore, the European hedgehog (*Erinaceus europaeus*). *Environmental Pollution*, 158(1), 161–166, https://doi.org/10.1016/j.envpol.2009.07.017

Eason, C. T., Milne, L., Potts, M., Morriss, G., Wright, G. R. G. & Sutherland, O. R. W. (1999). Secondary and tertiary poisoning risks associated with brodifacoum. *New Zealand Journal of Ecology*, 23(2), 219–224, http://www.jstor.org/stable/24054775

Eason, C. T., Wright, G. R. G., Milne, L. M. & Morriss, G. A. (2001). Laboratory and field studies of brodifacoum residues in relation to risk of exposure to wildlife and people. *Science for Conservation*, 177, 11–23.

ECHA, (2017). Biocidal products R4BP3. European_Chemicals_ Agency, Helsinki, Finland. Retrieved from https://echa.europa.eu/information-on-chemicals/biocidal-products

Eisemann, J. D. & Swift, C. E. (2006). Ecological and human health hazards from broadcast application of 0.005% diphacinone rodenticide baits in native Hawaiian ecosystems. In Proceedings of the 22nd Vertebrate Pest Conference https://doi.org/10.5070/V422110064

Fisher, P., Campbell, K. J., Howald, G. R. & Warburton, B. (2019). Anticoagulant rodenticides, islands, and animal welfare accountancy. *Animals*, 9(11), 919, https://doi.org/10.3390/ani9110919

Geduhn, A., Esther, A., Schenke, D., Gabriel, D. & Jacob, J. (2016). Prey composition modulates exposure risk to anticoagulant rodenticides in a sentinel predator, the barn owl. *Science of the Total Environment*, 544, 150–157, https://doi.org/10.1016/j.scitotenv.2015.11.117

Geduhn, A., Jacob, J., Schenke, D., Keller, B., Kleinschmidt, S. & Esther, A. (2015). Relation between intensity of biocide practice and residues of anticoagulant rodenticides in red foxes (*Vulpes vulpes). PLoS One*, 10(9), Article e0139191, https://doi.org/10.1371/journal.pone.0139191

Jacoblinnert, K., Jacob, J., Zhang, Z. & Hinds, L. A. (2022). The status of fertility control for rodents—recent achievements and future directions. *Integrative Zoology*, 17(6), 964–980, https://doi.org/10.1111/1749-4877.12588

Jurišić, A., Ćupina, A. I., Kavran, M., Potkonjak, A., Ivanović, I., Bjelić-Čabrilo, O., Meseldžija, M., Dudić, M., Poljaković-Pajnik, L. & Vasić, V. (2022). Surveillance strategies of rodents in agroecosystems, forestry and urban environments. *Sustainability*, 14(15), 9233, https://doi.org/10.3390/su14159233

Kotthoff, M., Rüdel, H., Jürling, H., Severin, K., Hennecke, S., Friesen, A. & Koschorreck, J. (2019). First evidence of anticoagulant rodenticides in fish and suspended particulate matter: spatial and temporal distribution in German freshwater aquatic systems. *Environmental Science and Pollution Research*, 26, 7315–7325, https://doi.org/10.1007/s11356-018-1385-8

Lefebvre, S., Fourel, I., Queffélec, S., Vodovar, D., Mégarbane, B., Benoit, E., Siguret, V. & Lattard, V. (2017). Poisoning by anticoagulant rodenticides in humans and animals: causes and consequences. In Malangu, N. (Ed.), Poisoning-From Specific Toxic Agents to Novel Rapid and Simplified Techniques for Analysis, 21. (Chapter 2) http://dx.doi.org/10.5772/intechopen.69955

López-Perea, J. J. & Mateo, R. (2018). Secondary exposure to anticoagulant rodenticides and effects on predators. In Van den Brink, N. W., Elliott, J. E., Shore, R. F. & Rattner, B. A (Eds.), Anticoagulant rodenticides and wildlife (pp. 159–193), https://doi.org/10.1007/978-3-319-64377-9_7

McMillin, S. C., Poppenga, R. H., Chandler, S. C. & Clifford, D. L. (2018). Anticoagulant Rodenticide Residues in Game Animals in California. Proceedings of the 28th Vertebrate Pest Conference.

Morzillo, A. T. & Mertig, A. G. (2011). Urban resident attitudes toward rodents, rodent control products, and environmental effects. *Urban Ecosystems*, 14, 243–260, https://doi.org/10.1007/s11252-010-0152-5

Olea, P. P., Sánchez-Barbudo, I. S., Viñuela, J., Barja, I., Mateo-Tomás, P., Pineiro, A. N. A., Mateo, R. & Purroy, F. J. (2009). Lack of scientific evidence and precautionary principle in massive release of rodenticides threatens biodiversity: old lessons need new reflections. *Environmental Conservation*, 36(1), 1–4, https://doi.org/10.1017/S0376892909005323

Pitt, W. C., Higashi, M. & Primus, T. M. (2011). The effect of cooking on diphacinone residues related to human consumption of feral pig tissues. *Food and Chemical Toxicology*, 49(9), 2030–2034, https://doi.org/10.1016/j.fct.2011.05.014

Quinn, N., Kenmuir, S. & Krueger, L. (2019). A California without rodenticides: challenges for commensal rodent management in the future. *Human–Wildlife Interactions*, 13(2), 8, https://doi.org/10.26077/gegq-dg52

Regnery, J., Friesen, A., Geduhn, A., Göckener, B., Kotthoff, M., Parrhysius, P., Petersohn, E., Reifferscheid, G., Schmolz, E., Schulz, R.S., Schwarzbauer, J. & Brinke, M. (2019). Rating the risks of anticoagulant rodenticides in the aquatic environment: a review. *Environmental Chemistry Letters*, 17, 215–240, https://doi.org/10.1007/s10311-018-0788-6

Stone, W. B., Okoniewski, J. C. & Stedelin, J. R. (1999). Poisoning of wildlife with anticoagulant rodenticides in New York. *Journal of Wildlife Diseases*, 35(2), 187–193, https://doi.org/10.7589/0090-3558-35.2.187

Wilson D. & Reeder D. (2005). Mammal Species of the World a Taxonomic and Geographic Reference (3rd ed.) The Johns Hopkins University Press; Baltimore, MA: Johns Hopkins University Press, Baltimore, Maryland, USA, 745–753.

Witmer, G. W. (2018). Perspectives on existing and potential new alternatives to anticoagulant rodenticides and the implications for integrated pest management. In Van den Brink, N. W., Elliott, J. E., Shore, R. F. & Rattner, B. A (Eds.), Anticoagulant rodenticides and wildlife (pp. 357–378), https://doi.org/10.1007/978-3-319-64377-9_13

Yu, Z. M., Chen, J. T., Qin, J., Guo, J. J., Li, K., Xu, Q. Y., Wang, W., Lu, M., Qin, X.C. & Zhang, Y. Z. (2020). Identification and characterization of Jingmen tick virus in rodents from Xinjiang, China. *Infection, Genetics and Evolution*, 84, 104411, https://doi.org/10.1016/j.meegid.2020.104411

Zakula, R. (1976). Game as a protein source. *Hrana i Ishrana*, 17, 543–548.