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Use of anticoagulant rodenticides in outdoor urban areas: considerations and proposals for the protection of public health and non-target species

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Abstract

Rodent control operations represent an important tool for the prevention and management of infestations, in outdoor environments, by synanthropic rodents (Rattus rattus and R. norvegicus), which are a source of economic and environmental damage with significant sanitary implications. Although the use of anticoagulants is safer to humans and pets compared to the use of acute poisoning substances, an intrinsic hazard of the active ingredients exists, i.e. the possible poisoning of non-target organisms (e.g., children, pets and wildlife) following exposure. The risks arising from the use of anticoagulants for rodent control operations in anthropic contexts can therefore only be mitigated by a proper selection of the active ingredient, bait formulation and administration techniques, since an active ingredient with selective action towards non-target species does not currently exist on the market.

This document lists practical proposals aimed at reducing the possibility of toxic exposure to anticoagulant rodenticides and mitigate the toxicological risk of human baits and non-target species.

Introduction

The identification of anticoagulants and their pharmacological/toxicological properties dates back to 1939 when, following a mass poisoning of bovine animals previously fed with silage and/or hay sweet clover, the hemorrhagic agent dicoumarol ($C_{19}H_{12}O_6$ - bisidrossicumarine) was identified as resulting from the metabolism of fungi colonizing the forage (1, 2). In 1948, a similar molecule called warfarin (3) was introduced as a rodenticide. With the arrival of anticoagulants around the 1950s, a gradual but radical transformation took place as these active ingredients gradually replaced the previous, acutely toxic substances such as strychnine, derivatives of chloral,

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phosphorus salts (mainly phosphides), arsenic, barium and red squill (4).

The introduction of anticoagulants has brought three major improvements in rodent control operations: i) the significant reduction of the toxicity of the bait, ii) the availability of an effective antidote in case of accident and iii) to overcoming of the "mistrust bait" reaction that takes place when a rodent (especially belonging to the *Rattus* genus) associates the death of a conspecific with the ingestion of a food matrix.

In homeoterm animals, anticoagulants act by blocking the synthesis of vitamin K in its functional form through inhibition of the vit. K enzymes epoxyd-reductase and, to a lesser extent, quinone-reductase.

Epoxid–reductase inhibition, due to the anticoagulants' action, is an obstacle to vitamin K epoxyde reduction, resulting in a inhibition of the vit. K regeneration.

Due to these inhibitions, the only vitamin K available to be reduced to vit. K hydroquinone is that introduced by food, which is quantitatively insufficient to warrant activation of coagulation factors.

Therefore, the absence of functional vitamin K involves blocking the carboxylation and consequent activation of clotting factors II, VII, IX and X (5-8).

The absorption of anticoagulants occurs mainly in the gastrointestinal tract after ingestion (9) and the symptoms, once the toxic dose is reached, do not occur until 24–48 hours, i.e. before the body has exhausted liver stocks of vitamin K and circulating active clotting factors.

Actions for rodent control in outdoor urban environments (public gardens, school environments, areas of public transit, etc.), commonly referred to as "rat extermination", are necessary for the protection of public health and are aimed primarily at contrasting the three synanthropic species *Rattus norvegicus* (Berkenhout, 1769) and *R. rattus* (L., 1758) and *Mus musculus* (L., 1758) (4).

Although the evolution of the active ingredients (AIs) was intended to reduce the acute toxicity and increase the efficacy of the commercial formulation of rodenticide; differently from acute toxic active ingredients, anticoagulants allow to reduce behavioral defense in target species.

It is necessary to clarify that no intervention of rodent control with the use of anticoagulant baits can be considered as fully safe.

This is due to the action of anticoagulants that are nonspecific and can affect all organisms with blood circulation; in addition, all urban or anthropic areas are sensitive to several variables that may affect the safety of the operation, including:

- the presence of sensitive population groups , including children under the age of 6 years, who are the most exposed (10);
- the need for interventions in highly frequented areas;
- the scarce or no surveillance of baits;
- the presence of non-target animal species (wild and domestic) (11), i.e. species at risk of direct (dog, hedgehog, water vole and other protected rodents) or indirect (mustelids, owls, birds of prey, cats, etc.) consumption of the active ingredient;
- the possibility, via non-target animals, of secondary and tertiary exposure due to ingestion of poisoned carcasses.

Due to the non-selective mode of action of anticoagulants, the reduction of potential risks to human health due to chemical rodent control using anticoagulants could be achieved through:

- regulation of amount of active ingredient and bait distributed;
- type of bait formulation;
- method of distribution / suitability of the formulation.

The objective of this paper is to provide an overview of safety issues concerning the use of anticoagulants in the management of rodents in urban areas and to draw up an operating method limiting the impact on public health and on non-target species.

Active ingredients

Anticoagulants are chemically classified according to the chemical structure of coumarins (dicoumarol derivatives) and indandiones (derivatives of 1,3- indandione) (12). Another classification could be based on the number of ingestions that are necessary to reach the effect on target species by reaching the lethal dose, namely, the fixation time of the active ingredient. Hepatic fixation time is closely related to the lipophilicity of the AIs (5, 7).

According to the latter type of classification, we can divide anticoagulants into:

• *first generation*, which includes AIs that require several ingestions to determine death and have a short fixation time (≈ 7 days) and a plasmatic half-life of about 18–55 hours (11); lots of active ingredients have been developed and used in the last decades, the most popular of these being chlorophacinone, coumachlor, coumafuryl (= fumarin), coumatetralyl, diphacinone and warfarin (= coumafene);

• *second generation*, which includes AIs that require a single ingestion to determine death and have a fixation time > 7–21 days and a plasmatic half-life of about 25–156 hours (11). Seven active ingredients belong to this group: brodifacoum, bromadiolone, difenacoum, difethialone, flocoumafen, pindone and valone.

Bait formulation

Bait formulation is critical, for both the palatability for the target species and safety for not-target species and humans. The bait represents the vehicle and is generally manufactured by food matrices and active ingredient, which this way is released into the environment and made available to the target species (13).

The type of formulation is pivotal for the assessment of the security of a rodent control system and the main problems are related to:

• size – small baits can be easily ingested and ingestion, particularly by children, can be silent (10);

• color – bold colors can easily attract the attention of children;

• texture – some paste formulations can be mistaken for modeling clay by children; this may lead to manipulation of the bait, even for long periods;

• taste – the presence of flavorings (vanilla, chocolate, etc.) can increase attractiveness to sensitive population groups and non-target species;

• possibility of anchoring and resistance to translocation – baits (e.g. cereals, caryopses, bags, etc.) can be easily translocated by rodents, thus constituting an additional risk factor.

The main formulations available on the market are summarized in Table 1, and critically analyzed for positive and negative aspects.

Distribution of baits

The distribution of baits in environments where signs of pest species have been detected, or in areas considered under risk of infestation, plays a pivotal role in preventing accidents to human and non-target animal species.

The main distribution techniques for baits can be summarized into two categories:

• uncontrolled distribution, with the random distribution of baits all around infested areas or the introduction of free baits into burrows (now forbidden by recent EU regulation about Biocides);

• controlled dispersion, which is the creation of bait stations where the bait is introduced in special containers (bait dispensers), accessible only to the target species.

With the controlled dispersion technique,

Table 1 - Main formulations available on the market

Type of formulation	Safety	
	pros	cons
Pellets (0.2 g) Small cubes (3.5 g)	limited AIs quantity per single pellet; difficult to translocate by rodents;	easily dispersed in the environment; easily ingested without chewing; impossible to fix to the bait station;
Flakes and grains (loose)	limited AIs quantity per single pellet; difficult to translocate by rodents;	easily dispersed in the environment; easily ingested without chewing; impossible to fix to the bait station; high palatability to cereal-feeding animals;
Flour (15 g sachets)	None in particular	easily dispersed in the environment; impossible to fix to the bait station;
Paste (12-15 g package)	None in particular	easily dispersed in the environment; easily ingested without chewing; impossible to fix to the bait station; attractivity to manipulation;
Paste (100 g trays)	difficult to translocate by rodents; easy to fix to the bait box;	high AI and bait quantity for each dispenser attractivity to manipulation; easily ingested without chewing.
Blocks (30-35 g) Sticks (100 g cylinders)	impossible to ingest without chewing; scarce attractivity to manipulation; easy to fix to the bait box; difficult to translocate by rodents.	reduced palatability when alternative food sources are present.

which is a technical evolution of uncontrolled distribution, the bait is placed within suitable containers (tamper proof) equipped with safe closures only accessible to target species.

Bait dispensers can be of various shapes, sizes and materials, but for use in an urban environment they should satisfy the following minimum requirements:

- be impact-resistant, i.e. usually made of plastic;
- not be of a flashy color;
- be equipped with locks systems that are not easily opened (e.g., not simply by pressure);
- have a system for anchoring the bait;
- be tamper proof.

It has been reported that the use of tamper-resistant bait stations allowed a substantial reduction in bait uptake by rodents when compared with unprotected baits or simpler protections (e.g. wooden material) (14). However, the use of tamper-resistant bait stations is mandatory in urban areas. In this regard, particular attention should be paid to the appropriate type of dispenser, keeping in mind the environment and target species.

Conclusions

The outdoor urban environments, and particularly sensitive areas such as playgrounds, school gardens, banks of rivers, sewer drains systems, degraded areas, etc., may require constant and continuous control of rodents involving the use of rodenticide baits.

In this context, each implementation of rodent control operations must be carefully designed, prioritizing safety and efficacy.

Based on the analysis of key operations in rodent control, as given in the introduction, toxicological impact in case of accidental exposure can be mitigated by adopting the following criteria based on the precaution principle:

• preferably, use of first-generation AIs. However, considering that first-generation anticoagulants are less and less sold and ineffective in many cases, opting for second-generation active ingredients characterized by a much lower LD_{50} value is almost mandatory. Among the second-generation anticoagulants, the use of bromadiolone, difenacoum and difethialone should be preferred. The use of brodifacoum should be very carefully evaluated because of its high toxicity to humans and non-target species, with the possibility of secondary and tertiary poisoning (7, 15-17);

• use formulations approved by the governmental authority; extemporaneously prepared baits should never be used, since they do not meet the minimum requirements of toxicological safety;

• avoid using formulations containing particularly attractive food flavorings (e.g. vanilla, chocolate);

• upload the dispenser with a quantity not greater than 50% of the LD_{50} g bait for a 10 kg boy (equivalent to the weight of a child or small-sized pet). In any case, more than 30-40 g of bait should not be placed in each dispenser. A more frequent refill of bait stations also allows more frequent safety checks and constant monitoring of murine population dynamics;

• use only solid formulations such as paraffin blocks and cylinders (sticks), which can be easily fixed to the dispenser. Absolutely do not use pellets and small cubes, the ingestion of which may go unnoticed (18);

• firmly anchor the bait dispensers through bolts or metal or plastic clamps. Avoid placement in areas subject to flooding;

• only use dispensers equipped with lock closure and not dispensers locked by simple pressure or other atypical protection systems (e.g. cover baits with a tile);

• avoid the use of bait in closed spaces (e.g. classrooms) as the dispenser may attract children's attention;

• limit bait use to a well-defined period of longevity of the toxic baits. The period should not be longer than 6 weeks per campaign (19). In urban environments, interventions against rats are frequent and the normal procedure is not to remove the empty dispensers until the following replacement, in order to avoid suspicion in the murine population.

The above operational measures allow to decrease exposure to the bait. Should the bait fall out of its container despite the above precautionary measures, it would still be difficult to ingest, unpleasant to handle, of an unpleasant taste and present only in small quantities. These baits would therefore only cause slight intoxications in non-target animals and humans, and would never be ingested in lethal doses.

Finally, areas subject to rodent control should be labeled by appropriate warnings informing on the type of action in progress, the active ingredient used and its concentration, the amount of bait in each dispenser and a telephone number for emergencies.

In conclusion, the use of bait formulations that are easily dispersible or removable by the target species (common in *Rattus* spp.), the placement of excessive amounts of bait in the dispenser, uncontrolled scattering of the bait, and the lack of appropriate (i.e., accurate information on toxicity to humans and domestic animals) risk communication, must be considered as malpractice.

Correct rodent control activities should focus primarily on the restoration of the environment through habitat management (4) and the reduction of food availability for rodents, rat proofing techniques and enhancement of wild predator populations, thus allowing a reduction of the environment's carrying capacity while limiting the use of rodenticides to situations where it is considered strictly necessary.

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Conflict of interest
The authors declare the absence of conflicts of interest.

Riassunto

Utilizzo dei rodenticidi anticoagulanti in aree urbane: considerazioni e proposte per la tutela della salute pubblica e delle specie no-target

Le operazioni di derattizzazione rappresentano una procedura importante per la prevenzione e la gestione delle infestazioni, negli ambienti aperti, da roditori sinantropi (*Rattus rattus* e *R. norvegicus*), i quali sono una fonte di danno materiale e di inquinamento biologico ambientale con importanti risvolti igienico-sanitari. Seppure l'impiego degli anticoagulanti risulti più sicuro nei confronti dell'uomo e degli animali domestici rispetto alle sostanze ad azione acuta, esiste comunque un pericolo intrinseco del principio attivo, che costituisce un fattore di rischio d'intossicazione per gli organismi non target (es. bambini, animali domestici e selvatici) in caso di esposizione. I rischi derivanti dall'utilizzo degli anticoagulanti nelle operazioni di derattizzazione nei contesti antropici possono essere dunque solo mitigati dalla corretta scelta del principio attivo, del formulato e delle tecniche di somministrazione, dato che attualmente non esiste in commercio un principio attivo che risulti selettivo per le specie target.

Nel presente documento vengono formulate alcune proposte operative volte a limitare la possibilità di esposizione all'agente tossico ed a ridurre il rischio tossicologico delle esche per l'uomo e per le specie non-target.

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