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ARTICLE

Prevalence of anticoagulant rodenticide poisoning in humans and animals in France and substances involved

PHILIPPE BERNY¹, JORDAN VELARDO¹, CORINE PULCE², ANDREA D'AMICO², MARTINE KAMMERER³, and ROMAIN LASSEUR¹

¹Department of Toxicology, Vetagro Sup-Campus vétérinaire

²Poison Centre of Lyon, Lyon 69424, France

³CAPAE-Ouest, Oniris-Nantes, Atlanpole La Chantrerie, BP40706, Nantes 44307, France

Introduction. Anticoagulant rodenticides have been used for over 50 years to control rodent populations. Since their first introduction, resistance developed in rodents, and second-generation products, more active but also more toxic, have been marketed. These compounds are currently being reviewed under European Regulations. **Methods.** The purpose of this work is to describe anticoagulant poisoning based on retrospective data from French human and animal poison control centers. Cases from 2004 to 2007 were collected. **Results.** Overall, the proportion of anticoagulant exposure reported to the Lyon poison control center appeared very limited and mostly occurred in young children, with no or very limited clinical severity. Some cases also occurred after intentional use of anticoagulants in adults. Circumstances of exposure are predominantly accidental in man (77%). In animals, both domestic and wild species, anticoagulant exposure seems more common, and often more accompanied by clinical signs. Among domestic species, dogs represent over 60% of the cases: in wildlife hares and rabbits account for almost 50% of the submitted cases, followed by predators and scavengers. **Conclusion.** Rodenticides involved are representative of the market share of anticoagulants, for human and domestic animal exposures. In wildlife, bromadiolone and chlorophacinone are by far the most important products, being the only ones registered for field use. There is no report of mortality in the human data, and less than 1% of all exposure cases in domestic animals were fatal.

Keywords Rodenticide; Anticoagulant; Retrospective survey

Introduction

Anticoagulant rodenticides have been used for several decades to control rodent populations worldwide. Warfarin was first marketed in the early 50s.¹ Unfortunately, several rodent species rapidly developed resistance to warfarin and other first generation anticoagulants. As a consequence, more potent second-generation anticoagulants were developed to overcome this resistance. These products are more toxic and active after only one feeding in rats.²

In France, rodenticides are currently licensed for use against household and field rodent species. First-generation products (chlorophacinone, coumatetralyl, warfarin), as well as second-generation products (brodifacoum, bromadiolone, difenacoum, difethialone, flocouma-

fen) are available against commensal rodents. Only chlorophacinone and bromadiolone are licensed for use outdoor and in the field in France.³ Anticoagulants are toxic to human beings as well as to many vertebrate species and very thorough reviews of their toxic doses and effects are available.^{2,4} Since the vitamin K pathway is common to humans and terrestrial vertebrate species, the clinical effects of anticoagulants are fairly similar across species, but susceptibility may vary greatly. Based on available toxicity data, the most susceptible species include rodents, hares and rabbits, swine, canids (dog, fox), mustelids (stoat), and birds of prey. The least susceptible species include many herbivores (ruminants, horses, etc.). Other species lie in between these two categories.²

Despite the availability of these general toxic data, few surveys or reports are available to evaluate exposures, or the extent of poisoning, to these compounds in man or animals.

Since anticoagulant rodenticides are currently being re-evaluated in the European Union, either as plant protection products (i.e. pesticides under the EU directive 91/414) or as biocidal products (for use in and around buildings under the EU directive 98/8), it seemed important to evaluate retro-

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Address correspondence to Prof. Philippe Berny, DVM, PhD, Department of Toxicology, Université de Lyon, Campus Vétérinaire de Lyon, 1 av Bourgelat, Marcy l'étoile 69280, France. E-mail: p.berny@vetagro-sup.fr

spectively poisoning with anticoagulant rodenticides in humans, domestic and wild animals before the marketing of new products, or the implementation of new mitigation measures, and thus to have a general overview of the current situation in France.

Methods

A retrospective survey of human and animal poisoning cases with anticoagulant rodenticides recorded between 1 January 2004 and 31 December 2008 was conducted.

Three different sources of data were used to retrieve suspected and confirmed anticoagulant poisoning incidents.

Human poison control center cases

The French Toxicovigilance Centers and Poison Control Centers have a common database, which was accessed from the Lyon Poison Control Center. The Poison Control Centers and Toxicovigilance Centers only receive calls from their geographical areas (central-eastern part of France in this case). For this reason, only data from the Lyon center (Lyon PCC) were used in this survey, but they account for 16% of the national database (estimation based on 2008 data) thus giving a reasonable overview of the nation-wide situation. Information regarding the patient's age, the circumstances of exposure, the active substance and type of rodenticide product, dose ingested as well as the severity of clinical signs and outcome were analyzed. Only human cases were retrieved. Calls involving therapeutic drug exposures were not included in the study. Cases assessed as confirmed anticoagulant poisoning had exposure, dose, and clinical data (time to onset of signs, clinical signs) consistent with published anticoagulant poisoning cases.

Animal poison control center cases

Data from the Centre AntiPoison Animal de l'Ouest (CAPAE) from the Nantes College of Veterinary Medicine were included in this survey. Basically, species, strain, age, circumstances of exposure, potential dose, severity, and outcome information (when available) were used. Due to financial limitations, there was no systematic follow-up of cases. Whenever outcome was available, it was entered in the database. Each case is assessed as a "not poisoning", "unlikely poisoning", "doubtful", "suspected poisoning" or "confirmed poisoning" based on history of exposure, dose of exposure, timeframe and clinical signs.

Wildlife toxicovigilance scheme

The Toxicology Laboratory of the Lyon College of Veterinary Medicine is a reference laboratory for

toxicological investigations in wildlife. A nation-wide disease surveillance system exists (SAGIR network) for the investigation of wildlife mortality.⁵ The network is based on the voluntary submission of dead animals to the local veterinary diagnostic laboratory, which in turn, will submit samples for toxicological investigation whenever necessary based on field information or necropsy. There is evidence that at least 10% of all animals found are submitted for necropsy, with special emphasis on suspected poisoning cases (Dr Lamarque, unpublished data). AVK analysis is conducted on either blood or liver samples using high performance liquid chromatography techniques with fluorescence and UV detection or mass spectrometry detection (for confirmatory purposes).⁶⁻⁸ The technique has been developed to monitor suspected cases for synthetic anticoagulant rodenticides (eight substances available in France) as well as some natural anticoagulants (ferulol and dicoumarol). All incoming cases are "suspected poisoning", while only those with detection of a given anticoagulant with consistent clinical/pathological findings will be classified as "poisoning" cases.

Marketshare of the active substances was estimated based on the number of licensed commercial products (data consistent with actual production, based on Liphatech estimation, Dr Lasseur personal communication).

Results

During the survey period, the Lyon PCC received 124,897 calls for suspected cases of human poisoning, among which 770 concerned anticoagulant rodenticides (i.e. 0.6%). Among them, only 280 were considered as poisoning cases (based on case history and dose ingested). No fatal outcomes were recorded. The age-distribution of patients is described in Fig. 1a. The majority of cases occurred in children, especially between 1 and 4 years of age (41% over the study period).

In CAPAE-OUEST, 14,145 suspected animal poisoning cases were recorded, among which 1269 concerned anticoagulant rodenticides (i.e. 8.96%). Symptomatic cases (evidence of hemorrhages, clotting disorders) represented 8.5% of these calls (108 cases). Mortality accounted for 0.6% of all anticoagulant poisoning cases at the time of the call (eight cases), but 7.4% of symptomatic cases. The age-distribution of poisoned animals is described in Fig. 1b. Since lifespan may be very different between species, age is reported as a category "young: not weaned animals", "juveniles: from weaning to reproductive stage", adult and elderly (>7 years in dogs, >8 years in cats).

Even though cases in animals were recorded mostly in adults (28%), the juvenile group appeared over-represented (9.9%).

At the Toxicology Laboratory of the Lyon College of Veterinary Medicine, 1750 wildlife cases were submitted for suspected poisoning, among which 476 were suspected anticoagulant rodenticide poisoning cases (27.2%). Antic-

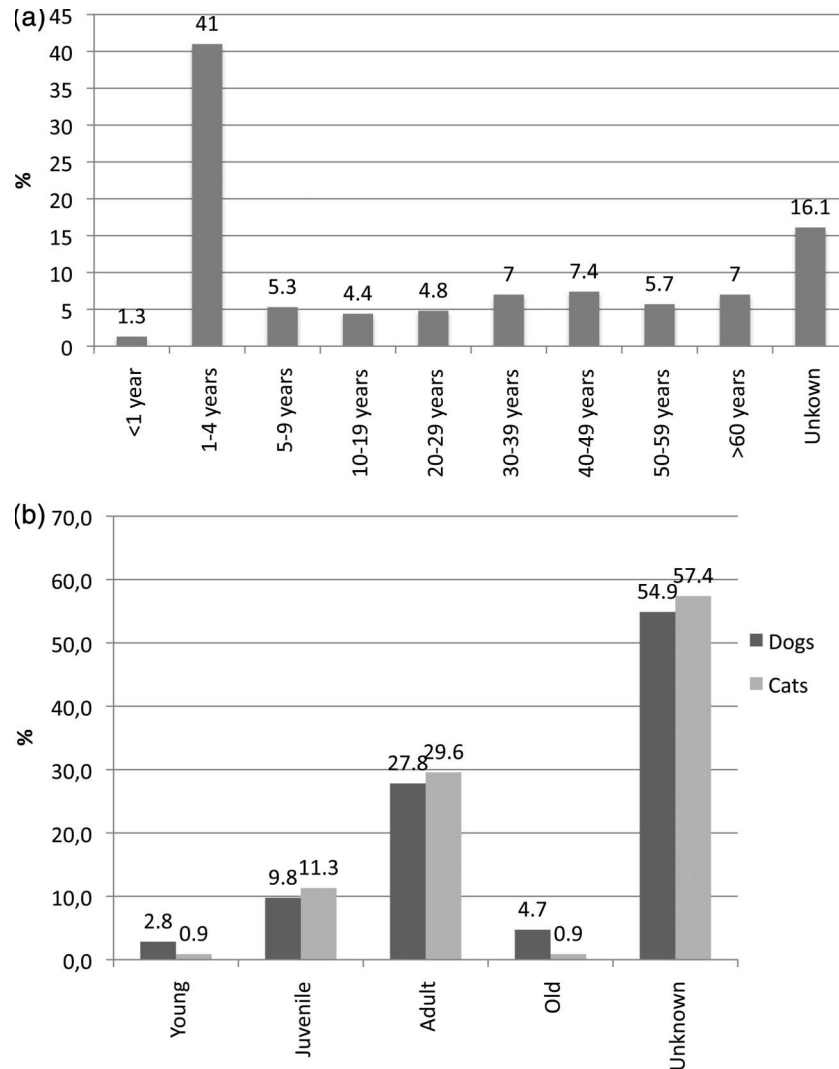


Fig. 1. Age distribution (%) of human beings (a, n = 770) and domestic animals (b, dogs, n = 953 and cats n = 115) exposed to anticoagulant rodenticides in France.

oagulant poisoning was eventually confirmed analytically in 185 cases (10.6% of all submitted cases). Since determining the age of a dead wild animal may be difficult for many species, this information was seldom reported and is not analyzed here.

For animals, species distribution is described in Table 1 (domestic species, CAPAE data) and b (wildlife). In domestic species, dogs and cats represent the vast majority of cases (84%). In wildlife, hares and rabbits are commonly found (almost 40%) and predators and scavengers are often poisoned as well (birds of prey and predators: 22%). Overall, birds are less commonly poisoned with anticoagulants, while they represent most of the cases submitted to the toxicology laboratory.⁹

The circumstances of exposure were retrieved from all three sources of data and are presented in Fig. 2a and b. In human beings, “voluntary exposure” included all cases of deliberate ingestion of a rodenticide (suicidal attempts, homicidal

Table 1. Species distribution of anticoagulant poisoned animals based on calls received at the CAPAE-Ouest (domestic) and at the Lyon’s Toxicology Laboratory (wildlife).

Wild Species	%	Domestic species	%
Hare/rabbit	39.7	Dog	75.1
Predators*	14.7	Cat	9.1
Wild boar	14.1	Poultry	3.3
Birds of prey	7.1	Horse	2.8
Roe deer	6.0	Sheep	1.2
Waterfowl	4.9	Goat	1.1
Pigeons	2.7	Cattle	1
Partridges	1.1	Ducks	0
Other	9.8	Rabbit	0
		Pig	1.4
		Other	5

*Predators include red foxes, small mustelids (stone marten, weasel...), wolves, and lynx.

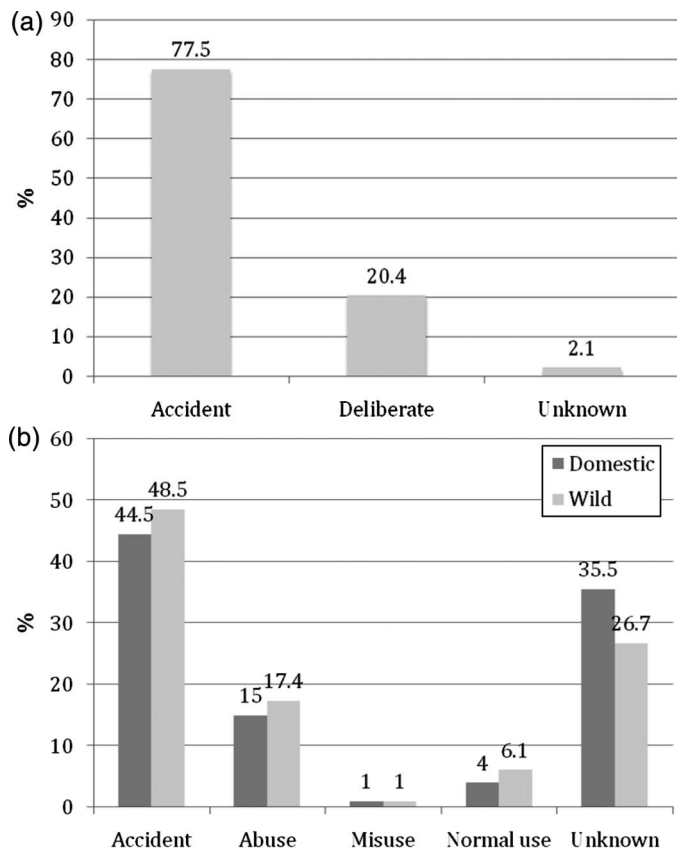


Fig. 2. Circumstances of poisoning in human beings (a, n = 770), domestic (b, n = 1068) and wild animals (b, n = 185) in France.

attempts for instance), “accident” included all accidental ingestions (child playing with a rodenticide box...), “unknown” included all cases for which there was no information on the circumstances of exposure. In animals, cases were defined as “normal use” when the rodenticide was used according to label and resulted in poisoning, “misuse” when the product was not used according to label, “abuse” when there was evidence of illicit and malicious intent (criminal baits for instance), “accident” when there was a known exposure (rodenticide box chewed on) but no specific information regarding the correct use of the rodenticide, “unknown” when all exposure information was lacking. Most cases were related to accidental ingestion (77%) of ready-to-use products (27%). The pattern of anticoagulant active substances involved is described in Fig. 3 for all three categories of victims (human, domestic and wild animals) as well as an estimate of the market share of the different anticoagulants in France. The active substance involved was obtained through case history (human data, animal poison control center data) and via analytical data (wildlife). There is a distinct pattern for each group in this study:

- In human beings, anticoagulants are usually identified (only 12.6% unknown anticoagulant) with difenacoum

(26.8%), chlorophacinone (21.4%), bromadiolone (11.4%), and difethialone (8.6%) accounting for most of the cases.

- In domestic animals, the exact anticoagulant involved is less commonly known (19.7% unknown anticoagulants), and most cases are recorded with difethialone (22.8), difenacoum (20.0%), brodifacoum (11.5%), and chlorophacinone/bromadiolone (10.9% each).
- In wildlife, the pattern is completely different with a vast majority of cases due to bromadiolone (45.3%), followed by chlorophacinone (9.2%), and difenacoum (8.8%).

The outcome of anticoagulant poisoning is seldom available: (91.2% unknown in human beings, 77.7% in domestic animals), but it should be remembered that anticoagulant rodenticide cases in humans are not routinely followed-up (in contrast to other suspected domestic poisoning cases). Only 280 cases considered potentially serious among the 770 total were followed, and there were no deaths. In dogs and cats, 0.6% of the cases report the death of at least one animal at the time of the call.

Discussion

Anticoagulant poisoning in human beings appears to be of moderate importance in our sample (less than 1% of the cases recorded), as is also seen in many countries worldwide.^{10–12} Children under 4 years are most commonly exposed, although it appears to a lesser extent than in the US.^{13,14} Current regulations in the US recommend bait placement out of reach of children but also, probably more efficiently, tamper-proof bait boxes are requested for second generation anticoagulants.¹⁴ In France, regulatory authorities request the use of bittering agents to reduce accidental bait intake by children. This could be one of the reasons for the relatively limited number of accidents in children in France and also for the absence of severe cases in children as well, although retrospective studies have not confirmed the preventive effect of the bittering agent denatonium benzoate.^{15,16} One major difference between US and French data lies in the respective proportions of intentional vs. accidental exposures: in the US¹³ 5.6% of the cases are intentional exposures compared to 20.4% in France. A Chinese study of fatal poisoning cases showed that rodenticides represent 19.7% of all compounds detected¹⁷ and suicidal attempts account for 51% of rodenticide poisoning cases. Severe outcome may occur in intentional exposures, with presumably higher doses ingested. The local availability of rodenticides may also affect these data. Thus tetramine and fluoroacetamide accounted for 90% of the lethal cases in China, although there has been a recent shift toward anticoagulant rodenticide use (in 2006–2008).

The situation is completely different in animals: anticoagulant poisoning is a major issue in veterinary clinical toxicology. This is also described in a 6-year study in

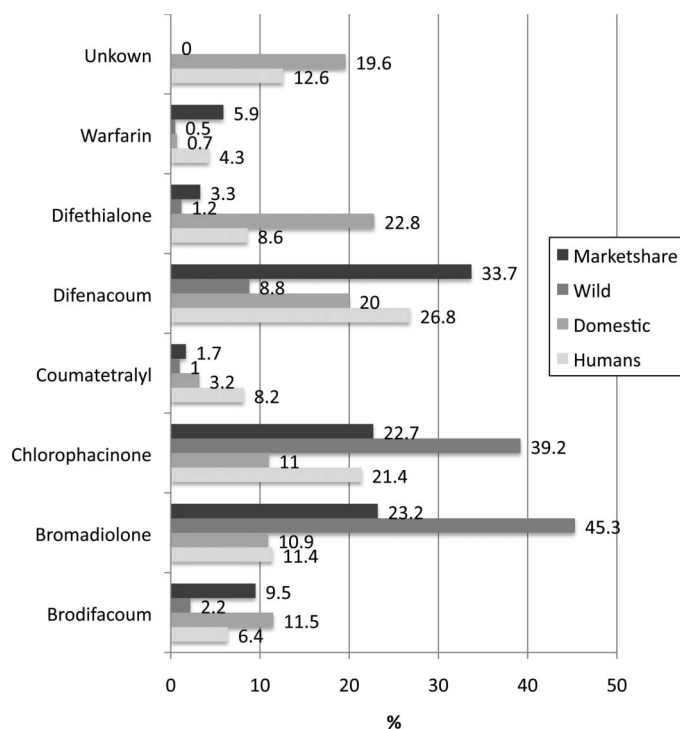


Fig. 3. Frequency distribution (%) of anticoagulant compounds exposure in human beings ($n = 770$), domestic ($n = 1269$) and wild animals ($n = 185$) compared with the market share of these compounds in France.

Austria¹⁸. Some species appear more at risk: dogs (among domestic species) and hares/rabbits, wild boars and foxes (all known to be highly susceptible^{2,6}). Some cases are described in cattle, sheep, and horses, all known to be poorly susceptible^{19,20} and to have normally only access to limited amounts of rodenticides.²¹ One potential explanation may be that anticoagulants are more toxic after repeated exposure, which may occur in a farm-environment.²⁰ Another explanation is the higher susceptibility of young animals,²¹ but the sample size was too small in this study to investigate the age distribution of cattle, sheep and horses. The proportion of “deliberate” (i.e. abuse) exposure in animals is quite high. Several authors report that illicit use of pesticides such as rodenticides generally occurs against animals considered as pests by these offenders.^{9,22–24}

Unfortunately, very few countries have established systems and procedures to document domestic and wild animal poisoning cases. In the European Union, the UK and France are among the few countries reporting those events on a regular basis but recent reports have suggested developing such a surveillance system EU-wide.^{9,25} Data available from the UK show a very similar picture, with a major concern for anticoagulant poisoning in wildlife, especially endangered species such as the Red kite (*Milvus milvus*).^{26,27}

The anticoagulants involved are quite different for each group of victims: in human beings, most cases are

associated with difenacoum and chlorophacinone and this distribution appears related to the market share of each anticoagulant, with some minor discrepancies (coumatetralyl and difethialone are over-represented for instance). Contrarily to what is reported in the US, comparatively few cases of brodifacoum ingestion are reported.^{10–13} In domestic species, the most toxic second-generation anticoagulants (brodifacoum, difethialone) are more involved than their market share would suggest over other compounds such as bromadiolone, difenacoum, and chlorophacinone. Since many cases are reported only when clinical signs occur, logically more toxic compounds will be overrepresented. In wildlife, the situation is completely different: only bromadiolone and chlorophacinone are licensed for use against field rodents in France. It was expected, therefore, to have a high proportion of cases associated with these two anticoagulants. Unexpected results, however, need to be pointed out: difenacoum, brodifacoum, or difethialone were also involved in some wildlife poisoning cases, despite their being prohibited for outdoor uses. As suggested by others,²² restrictions are not sufficient to ban a product or reduce the number of poisoning cases in wildlife: controlling distribution is a key issue as well, and it is rarely done, at least in many European countries. Studies on residues of anticoagulants in wildlife in Canada, in the UK, or elsewhere also show that many predator/scavenger species are contaminated by anticoagulants despite limited outdoor uses.^{23,27–29}

Most cases of exposure in human beings are not severe and do not result in any harmful outcome (98% in a review of US poison control center data^{10–13}). It has recently been stated that anticoagulants do not necessitate gastric decontamination or prophylactic Vitamin K administration^{13,30} and follow-up is even considered optional for most cases received at the Lyon Poison Control Center. Similarly, Caravatti et al.¹³ consider that accidental exposure in children is unlikely to result in a clinical event and do not recommend any specific action be taken. Only in intentional ingestion of superwarfarins is severe hemorrhagic disorder likely.³¹ Although less frequently than acute rodenticides such as tetramine or fluoroacetamide second-generation anticoagulant exposure is a common source of intentional ingestion leading to death (2009).¹⁷ It is noteworthy that no case of death could be attributed to anticoagulant rodenticide exposure in this study.

In domestic animals, there is a high proportion of cases with one animal dead, especially in those displaying clinical signs at the time of call. One key issue to understand the difference in severity between human beings and animals may be found in the analysis of circumstances of exposure: in human beings, only 2% of the cases occur under unknown circumstances, while the proportion reaches 35.5 and 26.7% in domestic and wild animals, respectively. This reflects the general lack of information on the circumstances of poisoning and, knowing that anticoagulants have a delayed onset of signs, poisoning is often suspected in animals only when clinical signs occur, hence the severity: in a previous study, it was shown

that >90% of the cases were reported between 6 and 48 h after exposure, i.e. long after induced vomiting may be of use.³²

Conclusions

Our data suggest that anticoagulant exposure in France is quite uncommon and usually benign in man. This may be the result of the addition of bittering agents and also of the limited concentration of anticoagulants available in most commercial products. Only intentional and repeated exposure seems likely to result in more severe outcome.

In domestic animals, clinical cases are more common, especially because exposure is not detected early and bleeding disorders may be quite important at the time of diagnosis. The compounds involved reflect the availability and toxicity of the active substances. Death is a frequent outcome. Prevention measures need to be refined in order to reduce the likelihood of exposure: tamper proof packaging should be mandatory for second-generation anticoagulants, limited packaging size for all other products should be considered. Reinforcing the role and services of pest control operators could also be advocated.

For wildlife, the use of anticoagulants may result in both primary poisoning and secondary poisoning in predators and scavengers. In France, chlorophacinone and bromadiolone are commonly detected in these cases, as they are the only active substances allowed for field uses, but our study reveals that other anticoagulants may be involved, thereby suggesting that illicit use of anticoagulants in the field occurs. This suggests a need for stricter delivery and control of bait used outdoors.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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