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MEMORANDUM

SUBJECT: Review of Incident Reports in Domestic Animals with the Anticoagulant Rodenticides Brodifacoum, Chlorophacinone and Diphacinone

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The data consulted for this review consisted of reports in the Incident Data System and the open veterinary literature.

Incident Data System

Brodifacoum

As of December 17, 1996, there were a total of 28 incidents for domestic animals involving brodifacoum in the Incident Data System (IDS). The majority of these were statistical summaries of calls to the National Animal Poison Control Center (NAPCC) concerning Enforcer® products. The summaries are for all of this registrant's products and span the period October 1993 to August 1996. The calls are categorized according to the likelihood that the product was responsible for the adverse reaction, i.e. high, medium, low, doubtful and exposure only. No information on animal species,

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clinical signs, or outcome of the incident are provided. It would be extremely labor intensive to compile the individual adverse incidents reported for each chemical. On brief review of the summaries, it is evident that most of the calls involved exposure only, i.e. the animal did not have clinical signs of illness.

There were ten reports on individual animals. Two cases were unrelated to brodifacoum exposure. In the other eight cases, a total of 8 dogs died and, one recovered with treatment.

Chlorophacinone

There were a total of 15 reports on domestic animals in IDS for chlorophacinone. The majority were statistical summaries of calls to NAPCC concerning Enforcer® products. The same problems exist with analyzing these data as described under **Brodifacoum**. On brief review, the majority of these calls also appear to be for exposures only.

There were three individual reports. All of them involved state investigations of dogs being poisoned accidently by rodenticides applied adjacent to the owner's property.

Diphacinone

There was only one report for domestic animals in IDS involving diphacinone. Two dogs died after possibly ingesting a product containing the chemical. The veterinarian indicated that the clinical signs and necropsy findings were consistent with diphacinone poisoning.

This number of reports of rodenticide poisonings is an underestimation of the true poisoning incidence rate in domestic animals. In general, registrants have not submitted the required 6(a)(2) reports on animals. Specifically, one of the registrants of a rodenticide, Mallinckrodt Veterinary, Inc., recently notified the Agency that a FIFRA audit by the company discovered unreported incidents.

Veterinary Literature Review

Comparative Toxicity

The anticoagulant rodenticides form two chemical classes, the hydroxycoumarins and the indanediones. The hydroxycoumarins consist of first and second generation anticoagulant types. The indanediones are also first generation anticoagulants. First generation refers to those chemicals which were found to be resistant in rodents; warfarin is the prototype for this class. The second generation chemicals are effective against warfarin-resistant rodents. A single-dose exposure of the second-generation anticoagulants is generally sufficient to cause fatality, whereas

repeated exposure is required for first-generation chemicals.[1]

Diphacinone and chlorophacinone are indanediones and first-generation anticoagulants, whereas brodifacoum is a second-generation chemical. Although diphacinone and chlorophacinone are first-generation anticoagulants, they differ from warfarin in that they are longer acting. The half-life for warfarin in the dog is 14.5 hours, whereas it is between 4 and 5 days for diphacinone in this species. Brodifacoum is also long-acting; the plasma half-life in the dog is approximately 6 days.[2]

Information on the relative acute toxicity of diphacinone and brodifacoum in dogs and cats, as compared to warfarin, is available. The following table is extracted from a recent article by Felice and Murphy.[2]

Table 1: Relative Toxicity of Three Anticoagulant Rodenticides in Dogs and Cats

		Acute Oral LD_{50}		
Chemical Name	Bait Concentration (ppm)	Compound (mg/kg) Dog	Compound (mg/kg) Cat	Bait* (oz/#) Dog
Warfarin	250	20-300	5-30	1.3
Diphacinone	50	0.9-8	15	0.3
Brodifacoum	50	0.2-4	25	0.06

* Ounces of finished bait per pound of body weight required to achieve the lowest LD_{50} reported in the dog.

The above table demonstrates several important comparisons of toxicity. First, diphacinone and brodifacoum are far more toxic in dogs than warfarin is. These chemicals have comparable toxicity in the cat. Second, warfarin is more toxic in the cat than the dog, whereas diphacinone and brodifacoum are more toxic in the dog.

Secondary poisoning is a greater hazard from the second-generation anticoagulants. As much as 100 gm of a 0.005% bait may be consumed by a Norway rat, providing enough brodifacoum to cause lethal poisoning in a small dog.[2]

All of the anticoagulant rodenticides inhibit the enzyme expoxide

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[1] Mount ME, Woody BJ, Murphy MJ (1986) The Anticoagulant Rodenticides. In Kirk RW (ed): Current Veterinary Therapy IX Small Animal Practice. Philadelphia, W.B. Saunders, pp. 156-165.

[2] Felice LJ, Murphy MJ (1995). CVT Update: Anticoagulant Rodenticides. In Bonagura JD (ed): Kirk's Current Veterinary Therapy XII Small Animal Practice. Philadelphia, W.B. Saunders, pp. 228-232.

reductase which is necessary to convert vitamin K expoxide to vitamin K. This depletes the body stores of vitamin K needed to convert precursor coagulation proteins to activated coagulation proteins. In general, there is a latent period of 2-5 days during which the stores are depleted before clinical effects are observed.[3] Toxicosis may be evidenced clinically by the classic signs of hemorrhage, including melena, epistaxis, hematuria, and bleeding from a venipuncture site. Other commonly observed signs include tachypnea and dyspnea. However, animals may occasionally die from anticoagulant rodenticide poisoning without external evidence of bleeding. On necropsy, there is evidence of internal hemorrhage into the body cavities.[2]

Most rodenticide poisonings are due to careless placement or overuse of baits, failure to discard poisoned rodents and malicious poisonings.[3] If the animal is observed ingesting a bait, emetics, adsorbents and cathartics may be helpful in preventing further absorption if given within 12 hours of ingestion. Vitamin K_1 is the specific antidote for anticoagulant rodenticide poisoning. Therapy must be maintained as long as vitamin K_1 epoxide is inhibited which may be as long as 3-4 weeks for the long-acting rodenticides diphacinone and chlorophacinone.[2] In comparison, the length of treatment for warfarin poisoning is only 4 to 6 days. Premature cessation of therapy can precipitate a hemorrhagic crisis.

The use of similar names for products containing different active ingredients can complicate treatment. The prognosis and cost of treatment is dependant on a knowledge of which chemical the animal has been exposed to. As stated previously, Vitamin K_1 therapy for warfarin poisoning is a much shorter duration than for the longer-acting anticoagulants. Examples of the confusion in product names follow. D-Con Mouse Prufe Kills Mice (Reg. No. 3282-9) contains warfarin, whereas D-Con Mouse Prufe II Kills Mice contains brodifacoum. Enforcer Mouse Kill II (Reg. No. 10182-93-40849) contains brodifacoum, whereas Enforcer Mouse Kill III (Reg. No. 7173-188-40849) contains bromodiolone.

Incident Reports from the Veterinary Literature

The NAPCC is a 24-hour service located at the University of Illinois which receives calls concerning animal poisonings from veterinarians, human poison control centers, government agencies, and animal owners. The certainty of an association between the suspected agent (pesticide, drug, plant, etc.) and the poisoning is assigned to each case. The certainty categories applicable to companion animals were toxicosis, suspected toxicosis, doubtful

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[3] Reid FM, Oehme FW (1989). Toxicoses. In Sherding RG (ed): The Cat: Diseases and Clinical Management. New York, Churchill Livingston, Inc., pp. 185-215.

toxicosis, exposure, and information only.[4]

NAPCC has periodically published yearly reports in the veterinary literature. The following is a summary of the incidence of pesticide-related calls. In 1984, the Center received almost 8000 calls regarding dogs and cats. After insecticides, rodenticides were the most prevalent category of agents. NAPCC postulated that the reasons for the prevalence of this class of pesticides were: 1) rodenticides are often placed in areas in which both rodents and pet animals are present; and 2) the NAPCC has an agreement with the manufacturers of the anticoagulant brodifacoum so that their telephone number is on products containing this chemical. Regardless of the chemical involved, the vast majority of anticoagulant rodenticide calls were for exposure only (no clinical signs of toxicity).[5]

The number of calls to NAPCC increased to roughly 20,000 in 1986 and 25,000 in 1987. In the yearly report for 1986, details on the number of calls by toxicant class and individual toxicant were provided. The top three classes of toxicants involved in the 14,721 calls concerning dogs were rodenticides (22.7% of all calls), human medicines (17.0%) and insecticides (12.0%). Of the rodenticide calls, 77.6% were categorized as exposure only. Brodifacoum was the number one generic agent involved in canine calls; 83.9% of the 2058 calls concerning this chemical were exposure only. Diphacinone was number 17 in the generic ranking for dogs.[6]

There were 5075 calls of poisonings in cats in 1986. The top three toxicant categories were insecticides (25.7% of all calls), plants (21.4%) and human medicines (9.9%).[6] However, brodifacoum was number 2 in the generic ranking for cats.[6]

A very short article on the top 25 generic agents involving dogs and cats for which the NAPCC received calls in 1992 was recently published. During this year, 12,611 cases involving one or more dogs and 5351 cases involving one or more cats were evaluated. Of the top 15 generics for dogs, brodifacoum and diphacinone were number one and two; none of the rodenticides were on the list for cats. No data were provided on how many calls were classified as

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[4] Hungerford LL, Trammel and Clark MJ. The potential utility of animal poisoning data to identify human exposure to environmental toxins. *Vet Human Toxicol*, 1995; 37:158-162.

[5] Beasley VR (1986) Prevalence of poisonings in small animals. In Kirk RW (ed.) Current Veterinary Therapy IX Small Animal Practice. Philadelphia: WB Saunders Co., pp. 571-590.

[6] Beasley VR (1986) Incidence of Poisonings in Small Animals. In Kirk RW (ed.) Current Veterinary Therapy IX Small Animal Practice. Philadelphia, WB Saunders Co., pp. 571-590.

exposure only.[7]

The American Association of Poison Control Centers (AAPCC) reported 41,854 animal exposure cases in 1990. The AAPCC has no mechanism for collecting species-specific information. However, based on a sample of cases, it is assumed that 99% of the animal cases represent poisonings in companion animals with about 75% in dogs, 20% in cats and 4% in other pets. The leading types of products responsible for the 454 deaths in 1990 were ethylene glycol and related compounds (9.6% of deaths), anticoagulant rodenticides (9.2%) and organophosphates (7.3%).[8]

CONCLUSIONS

The anticoagulant rodenticides are cause serious and costly poisonings in domestic animals, especially dogs. Secondary poisonings through consumption of poisoned rodents is also a concern. Although most of the reports to the NAPCC were for exposure only and clinical signs were not evident, there still may be significant cost to the pet owner in diagnostic tests and monitoring.

RECOMMENDATIONS

1. On cursory review of product labels containing these rodenticides, most contained Caution statements to keep product away from humans, domestic animals and pets. OREB recommends that the labels also contain statements in the Caution section to instruct users of the product to remove poisoned rodents from areas accessible to domestic animals. As indicated in the review, this is a source of poisoning for pets.

2. Under Note to Physicians, many of the labels recommend that Vitamin K_1 be administered intravenously (IV) or intramuscularly (IM). The veterinary literature states that Vitamin K_1 can cause anaphylactic reactions if given IV and extensive hemorrhage after IM administration. Sheldon Wagner, M.D., a consultant to OPP, confirmed that Vitamin K_1 should not be given IV unless there is a hemorrhagic crisis. IM administration is acceptable in humans. The recommendation for IV administration should be deleted from the label.

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[7] Buck WB (1995) Top 25 Generic Agents Involving Dogs and Cats Managed by the National Animal Poison Control Center in 1992. In Bonagura JD (ed.) Current Veterinary Therapy XII Small Animal Practice. Philadelphia, WB Saunders Co., p. 210.

[8] Hornfeldt CS, Murphy MJ (1992) Poisonings in Animals: A 1990 Report of the American Association of Poison Control Centers. Veterinary Human Toxicology 34(3):248-250.