To Whom It May Concern:

The Department of Pesticide Regulation (DPR) is proposing to amend sections 6000 and 6400, and adopt section 6471 of Title 3, California Code of Regulations (3 CCR). The proposed action would designate the active ingredients brodifacoum, bromadiolone, difenacoum, and difethialone as California-restricted materials, making all second generation anticoagulant rodenticide (SGAR) products restricted materials. Also, this proposed action would add additional use restrictions for SGARs, and revise the definition of private applicator to refer to the federal definition of agricultural commodity found in Title 40, Code of Federal Regulations (40 CFR) section 171.2(5).

While the intent of the proposed changes is to minimize the potential adverse effects of SGAR on domestic pets, children, and wildlife, it is likely that the proposed restrictions on the use of SGAR will not achieve the desired outcomes. In fact restricting the use of SGAR will increase the risk of domestic pet exposure to and intoxication from first generation anticoagulant rodenticides (FGAR) such as diphacinone and, perhaps more importantly, from alternative, non-anticoagulant rodenticides such as bromethalin and cholecalciferol. In addition, there is insufficient scientific information available to conclude that the proposed restrictions on the use of SGAR by licensed individuals in agricultural settings will significantly decrease primary or secondary exposure of wildlife to these compounds. While it is true that residues of SGAR (and FGAR) are frequently detected in a variety of wildlife species, the pathways of exposure are often unknown. Also, the mere presence of an SGAR in an animal cannot be interpreted as an adverse effect. Thus, exposure frequency (as opposed to intoxication frequency) cannot be used to assess or predict adverse effects at a population level.

I am troubled by the imposition of potentially far-reaching regulatory actions that are not based upon a sound scientific foundation. An example of a lack of sound science was the statement made by a senior DPR scientist who wrote that “the data also show that exposure of wildlife to second generation anticoagulant rodenticides can lead to sub-lethal effects” in a memorandum to the Pesticide Registration Branch dated June 27, 2013. There is no basis for this statement and it is absolutely misleading. The author cites a bobcat study conducted by Riley et al. (2007) that found a strong correlation between SGAR liver residues and the occurrence of severe notoedric mange. In my view this was a false statistical correlation between two high frequency events in the studied population and which has no mechanistic basis to support it. Another troubling interpretation of data occurred when SGAR LD_{50} values were compared to their respective liver concentrations found in dead wildlife. Such a comparison is meaningless and is analogous to comparing “apples to oranges”.

Adverse consequences associated with restricting SGAR use, along with a corresponding increased use of alternative rodenticides such as bromethalin and cholecalciferol (and off-label use of zinc phosphide), have not been adequately addressed by the DPR. This is particularly true with regard to increased risks to domestic pets (i.e., dogs and cats). As a veterinary toxicologist with over 25 years of experience dealing with the impact of rodenticides on pets, I offer the following comments:

1) There are substantial limitations to the data collected through incident reporting mechanisms.

While exposure of dogs to anticoagulant rodenticides is commonly reported in the veterinary literature (Schaer and Henderson, 1980; Bellah and Weigel, 1983; Stowe et al., 1983; Schulman et al., 1986; DuVall et al., 1989; Woody et al., 1992; Peterson and Streeter, 1996; Hornfedt and Phearman, 1996; Lewis et
doses as low as 0.1 mg/kg are reported to cause clinical signs in cats. Young animals are considered to be tolerant to oral doses as low as 0.1 mg/kg.

However, oral doses as low as 0.1 mg/kg are reported to cause clinical signs. These toxicity data are useful for understanding the relative safety of different rodenticides for pets.

Minimum lethal doses for cats and dogs are 0.45 mg/kg body weight and 2.5 mg/kg body weight, respectively. Reported lethal oral doses of cholecalciferol for dogs are variable, with little acute toxicity data available for cats. Gupta (2012) reports lethal intoxication of dogs at doses as low as 2 mg/kg. However, oral doses as low as 0.1 mg/kg are reported to cause clinical signs. These toxicity measures are in sharp contrast to a reported oral LD50 dose for dogs of 88 mg/kg. Like dogs, toxic oral doses as low as 0.1 mg/kg are reported to cause clinical signs in cats.
be more sensitive to cholecalciferol than adult animals. Lethal oral doses of zinc phosphide for dogs and cats are similar, with 40 mg/kg body weight given for both (Albretson, 2004).

With respect to the potential for secondary intoxication of either dogs or cats resulting from the ingestion of SGAR poisoned rodents, no case reports could be found to confirm this possibility. While cats might be at risk of secondary intoxication from ingestion of bromethalin-poisoned target or non-target species, there is little data available to judge the likelihood of this occurring under field situations. In dogs, no adverse effects were noted in a limited number of animals given ground meat from rats fed bait containing 0.005% bromethalin for 1 day. Dogs developed partial anorexia and lethargy following the consumption of possums poisoned with an LD50 dose of bromethalin when exposed for 5 days (USEPA, 2004). Although it has been suggested that secondary intoxication of pets following the field use of cholecalciferol-containing products might occur, little data is available to support or refute this statement. Based upon rather limited data, adverse effects have been reported in dogs and cats following consumption zinc phosphide-poisoned nutria or voles fed bait containing 5% zinc phosphide (USEPA, 2004).

Concern about the possibility of secondary poisoning following consumption of SGAR poisoned rodents by non-target animals relates to poisoned rodents ingesting a “superlethal” dose of SGAR with subsequent high carcass residue concentrations. Although SGAR are designed to kill target rodents following a single feeding, the delay in onset of clinical signs and death (2 to 4 days) is believed to allow continued bait ingestion during the latent period resulting in high tissue residue concentrations. The likelihood of ingestion of “superlethal” doses of non-anticoagulant rodenticides, particularly bromethalin and cholecalciferol, has not been adequately investigated. Data limitations with regard to exposure doses associated with the ingestion of animals poisoned by these two alternative rodenticides would appear to preclude a proper risk assessment.

When discussing potential adverse effects of non-anticoagulant rodenticides on dogs and cats, it is important to point out the potential human health risk from inhalational exposure to phosphine gas following spontaneous vomiting associated with zinc phosphide ingestion. Performing decontamination of exposed animals also presents a potential human health risk. In a large retrospective case series, approximately 2/3 of dogs exposed to zinc phosphide developed gastrointestinal signs including vomiting (Gray et al., 2011). Intentional gastric emptying (emesis induction or gastric lavage) was performed in approximately ¼ of the cases. Between spontaneous vomiting and intentional gastric emptying, a large number of pet owners or veterinary staff are potentially exposed to phosphine gas. Occupational phosphine gas poisoning has been documented in veterinary staff treating dogs that ingested zinc phosphide (Schwartz et al., 2012).

3) The delay in onset of clinical signs following ingestion of toxic doses of FGAR and SGAR provides an opportunity for medical interventions that is less likely following ingestion of more rapidly acting non-anticoagulant rodenticides such as bromethalin and zinc phosphide.

There is typically a 2 to 4 day delay in onset of clinical signs following ingestion of a toxic dose of either FGAR or SGAR anticoagulant rodenticide. This delay provides some flexibility with regard to how rapidly an animal needs to be presented to a veterinarian following a known exposure. Such a delay might be beneficial in situations where discovery of ingestion is not immediate (e.g., an opened or chewed package or bait discovered after an owner returns home from work).

In contrast, non-anticoagulant rodenticides such as bromethalin, cholecalciferol, and zinc phosphide can have a much more rapid onset of clinical signs, thus requiring more rapid veterinary intervention. Thus,
there is a shorter window of opportunity for seeking veterinary attention for non-anticoagulant rodenticide exposures compared to anticoagulant rodenticide exposures. Unfortunately, it is possible that an animal might die from bromethalin or zinc phosphide ingestion during the absence of an owner at work.

Interestingly, the EPA cites a study by Cope et al. (2006) in which the average exposure time to treatment time following toxicant exposure by pets was approximately 7-1/2 hours. This length of time severely limits the effectiveness of standard decontamination procedures (e.g., induction of emesis, gastric lavage, or activated charcoal administration) following exposure to most toxicants. The important point is that such a delay in presentation does not negate effective treatment (vitamin K₃ administration) following anticoagulant rodenticide exposure, but might severely limit the effectiveness of treatment following bromethalin or zinc phosphide intoxication (for which no antidotes are available) given the relatively rapid onset and progression of clinical signs for the two rodenticides.

Table 1: Comparative time to onset of clinical signs following ingestion of a toxic dose of rodenticides.

<table>
<thead>
<tr>
<th>Rodenticide</th>
<th>Time to Onset</th>
</tr>
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<tbody>
<tr>
<td>FGAR and SGAR</td>
<td>2 to 4 days</td>
</tr>
<tr>
<td>Bromethalin</td>
<td>2 to 24 hours; delayed onset of clinical signs with lower doses possible</td>
</tr>
<tr>
<td>Cholecalciferol</td>
<td>12 to 36 hours</td>
</tr>
<tr>
<td>Zinc phosphide</td>
<td>15 minutes to 4 hours; may be delayed for up to 18 hours</td>
</tr>
</tbody>
</table>

4) The cost and complexity of treatment of non-anticoagulant rodenticide intoxicated pets is potentially much more than for anticoagulant rodenticides.

Brutlag and Hovda (2011) comprehensively discussed these concerns in their report. However, it is important to re-emphasize that there are no specific antidotes available for non-anticoagulant rodenticides, in contrast to anticoagulant rodenticides for which vitamin K₃ is effective and inexpensive. Anticoagulant rodenticide-exposed/intoxicated animals can be treated effectively at home following an initial assessment by a veterinarian due to the relative ease of administering vitamin K₃ in a home environment. This is not possible following exposure/intoxication with non-anticoagulant rodenticides; treatment of symptomatic animals generally requires intense in-hospital treatment with multiple drugs.

Pachtinger et al. (2008) demonstrated that simple and standard decontamination procedures (inducing vomiting and given activated charcoal orally) in anticoagulant rodenticide-exposed dogs resulted in no additional treatment being needed in more than 90% of the cases. This indicates that in the majority of known anticoagulant rodenticide ingestions, timely decontamination can ameliorate the need for further treatment and minimize the cost of treatment. Unfortunately, similar studies have not been conducted for non-anticoagulant rodenticides.

The FIFRA Scientific Advisory Panel (USEPA, 2011b) suggested that the EPA did not sufficiently consider the societal cost of treating animals (pets and wildlife) intoxicated by non-anticoagulant rodenticides. The Panel stated that “generally speaking cost of treatment is higher, and the prognosis is lower, for non-anticoagulant rodenticides compared to the anticoagulant rodenticides”. The lack of specific antidotes for non-anticoagulant rodenticides results in the need for general symptomatic and supportive care of intoxicated animals. This can be quite involved given the complex pathophysiologic effects of these alternative rodenticides (Peterson, 2013; Peterson and Fluegeman, 2013). For example, metastatic tissue calcification following intoxication by cholecalciferol affects multiple organ systems
including the cardiovascular, gastrointestinal, and renal systems. In addition, the potential for persistent or chronic effects following widespread metastatic tissue calcification following cholecalciferol intoxication or severe central nervous system edema following bromethalin intoxication is greater than for anticoagulant rodenticides.

5) The availability of diagnostic tests to detect intoxication by non-anticoagulant rodenticides is quite limited compared to anticoagulant rodenticides.

The FIFRA Scientific Advisory Panel indicated that the consequences associated with increased use of bromethalin “are unknown and worrisome due to the lack of diagnostic tests” to confirm exposure/intoxication. This concern is well-founded. Specific diagnostic tests to confirm exposure/intoxication to anticoagulant rodenticides are widely available at many veterinary diagnostic laboratories. In contrast, there are few laboratories that provide testing for bromethalin, cholecalciferol, or zinc phosphide (the breakdown product, phosphene, is universally measured in lieu of measuring the parent compound). Only the veterinary diagnostic laboratory at UC-Davis offers a test for the toxic metabolite of bromethalin, desmethylbromethalin, on antemortem and postmortem samples. Unfortunately, bromethalin cannot be reliably detected in antemortem and postmortem samples such as blood, serum, or urine. Confirmation of bromethalin intoxication is typically made postmortem. To my knowledge, there are only two laboratories (one veterinary diagnostic laboratory and one private non-veterinary laboratory) offering testing for cholecalciferol and/or metabolites.

The following table summarizes the availability of diagnostic testing for anticoagulant and non-anticoagulant rodenticides from ten veterinary diagnostic laboratories offering toxicology testing.

Table 2:

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Anticoagulant Rodenticides</th>
<th>Bromethalin (or metabolite)</th>
<th>Cholecalciferol (or metabolite)*</th>
<th>Zinc Phosphide (phosphine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAHFS (CA)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Iowa State VDL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Michigan State VDL</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Washington State VDL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Purdue ADDL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cornell VDL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Texas A&amp;M VDL</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PADLS (PA)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kentucky - Lexington</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Refer samples to private laboratory in IA for testing.

Thus, testing for anticoagulant rodenticides is widely available, testing for zinc phosphide is moderately available, while testing for bromethalin and cholecalciferol is limited.

It is important to point out that both national animal poison control centers have expressed concerns about the impact of the USPEA mitigation measures on the risk to pets of the use of alternative rodenticides. These concerns are applicable to the proposed DPR mitigation measures as well.
Conclusions

- There is good reason to believe that the mitigation measures for non-anticoagulant rodenticide products will not achieve the intended results. There is likely to be an increased risk of morbidity and mortality to pets due to increased use of non-anticoagulant rodenticides (particularly bromethalin and cholecalciferol) for which no specific antidotes exist and for which treatment is more complicated and costly. Cats, in particular, are at potentially increased risk since they are relatively resistant (compared to dogs) to anticoagulant rodenticides (anticoagulant rodenticides) compared to available alternatives, particularly bromethalin.
- Without a history of known exposure to non-anticoagulant rodenticides products, the diagnosis of pet exposure/intoxication is more difficult due to the lack of cost effective and timely diagnostic tests.
- The proposed mitigation measures appear to be extreme given current data gaps and potential problems associated with the use of alternative non-anticoagulant rodenticides. It would seem that one or more pilot studies could have been conducted in geographically restricted environments to better assess the impact of various and less severe mitigation.

References


Respectfully submitted,

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