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FARAD Digest

Mechanisms of toxicity and residue considerations of rodenticide exposure in food Animals—a FARAD perspective

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The Food Animal Residue Avoidance Databank (also known as the Food Animal Residue Avoidance and Depletion Program; FARAD) frequently receives requests for withdrawal interval (WDI) recommendations following inadvertent exposure of food animals to various environmental contaminants and pesticides such as rodenticides **(Table 1)**. Rodenticide exposure in food animals typically occurs as a result of widespread use on farms for rodent control, contamination of waterways, or malicious intent. The Environmental Protection Agency (EPA) is the regulatory body that oversees rodenticides in the US, with 11 rodenticide chemicals currently carrying numerous active commercially registered products. The principal challenges when recommended WDIs are formulated for animals exposed to anticoagulant rodenticides and rodenticides with other mechanisms of action are numerous. These challenges include a lack of robust tissue pharmacokinetic data (particularly limited tissue half-lives) in many species, the low number of animal subjects enrolled in pharmacokinetic studies that may not represent population variations, and incomplete knowledge of dose exposure in affected animals. For most rodenticides, marker residues can be present in tissues such as the liver, pancreas, and kidney for years following oral exposure, whereas other more commonly consumed tissues may have declining residues over a period of months. Therefore, despite clinical resolution of rodenticide toxicosis in affected animals, extremely protracted WDIs should be anticipated for food animals exposed to rodenticides. Cases involving food animals exposed to rodenticides are complex, given that the potential to produce violative residues in edible tissues is a function of such widely variable factors as dose, length of exposure, chemical and product type, toxicokinetic properties, animal age, and time to market. Therefore, we encourage veterinarians to contact FARAD to formulate a data-driven WDI recommendation following a rodenticide exposure in any food animal species.

Anticoagulant rodenticides

Classifications

Anticoagulant rodenticides can be classified by potency (first generation vs second generation) or chemical structure. First-generation anticoagulant rodenticides (FGARs) are considered less potent than second-generation anticoagulant rodenticides (SGARs). This is due to the short half-lives of FGARs, which require continuous feeding to targeted pests to have the desired effect. First-generation anticoagulant rodenticides typically undergo extensive metabolism resulting in polar metabolites that are excreted via the urinary system. However, FGARs are subject to increasing resistance in mice and rats worldwide through development of single nucleotide polymorphisms in the vitamin K epoxide reductase complex subunit 1 gene leading to greater us-

Table 1— Food Animal Residue Avoidance and Databank Program (FARAD) submissions for rodenticide exposure in food animals in the US between January 1, 1999, and July 14, 2021.

Compound	Category	No. of active EPA registrations	No. of FARAD submissions	Chickens	Swine	Goats	Beef cattle	Sheep	Dairy cattle
Brodifacoum	SGAR	38	23	10	8	2	2	0	1
Bromadiolone	SGAR	67	24	12	8	4	0	0	0
Bromethalin	NAR	190	17	8	5	2	1	1	0
Cholecalciferol	NAR	17	0	0	0	0	0	0	0
Chlorophacinone	FGAR	50	1	0	1	0	0	0	0
Difenacoum	SGAR	1	0	0	0	0	0	0	0
Difethialone	SGAR	31	3	0	3	0	0	0	0
Diphacinone	FGAR	144	9	4	3	1	1	0	0
Strychnine	NAR	21	1	1	0	0	0	0	0
Warfarin	FGAR	23	6	3	2	0	0	1	0
Zinc phosphide	NAR	102	0	0	0	0	0	0	0
Total			**84**	**38**	**30**	**9**	**4**	**2**	**1**

FGAR = First-generation anticoagulant rodenticide. NAR = Nonanticoagulant rodenticide. SGAR = Second-generation anticoagulant rodenticide.

Table 2—Plasma and tissue half-lives for various rodenticides for which plasma or tissue half-lives have been established in food animal species.

Rodenticide	Class	Half-life (h)	Species; tissue	Reference number
Warfarin	FGAR	49.28	Chicken; egg white	15
		16–17	Swine; plasma	10
		9.49	Sheep; plasma	12
Coumatetralyl	FGAR	348–655.2	Cervids; liver	16
Pindone	FGAR	96–120	Sheep; plasma	19
Diphacinone	FGAR	194.4–504	Swine; liver	16
Chlorophacinone	FGAR	30.13	Sheep; plasma	12
Brodifacoum	SGAR	27.4	Chicken; plasma	32
		127.2	Chicken; muscle	32
		1,510–1,671	Sheep; liver	31
Bromadiolone	SGAR	718–1,091	Swine; liver	34, 35
		49.5	Sheep; plasma	12
Flocoumafen	SGAR	> 2,400	Quail; liver	42
		> 3,000	Sheep; plasma	19

See Table 1 for key.

age of SGARs.[1] Second-generation anticoagulant rodenticides are not readily metabolized and undergo substantial enterohepatic recirculation prior to fecal excretion, resulting in the persistence of these drugs in the body. Furthermore, SGARs remain persistently bound in a stable form to the endoplasmic reticulum membrane protein and vitamin K epoxide reductase and in microsomes of the liver, kidney, or other target tissues, leading to a prolonged elimination half-life from target organs, a process that is not reflected by plasma concentrations.[2] The persistence of SGARs in target organs is dependent on chemical structure and compound and the ratio of stereoisomers within the product in question.[2,3] In general, anticoagulant rodenticides are highly bound to plasma protein (as high as 99% for warfarin), and therefore concomitant administration of other drugs that are highly bound to plasma protein, such as phenylbutazone, flunixin meglumine, corticosteroids, or sulfonamides, may potentiate toxicosis through increasing the free fraction of rodenticides.[4]

The 2 major chemical classifications of anticoagulant rodenticides are hydroxycoumarins and indanediones. Hydroxycoumarins are distinguished by the presence of a 4-hydroxycoumarin ring, with a variety of substituents present at position 3.[5] Members of this group include FGARs (warfarin, coumafuryl, and coumatetralyl) and SGARs (bromadiolone, brodifacoum, and difenacoum). Meanwhile, the indanedione group is characterized by a 1,3-indanedione structure with a variety of substituents at position 2.[5] There is some confusion as to the classification of members of this group as FGARs or SGARs; indanediones include pindone, chlorophacinone, and diphacinone.

First-Generation Anticoagulant Rodenticides

First-generation anticoagulant rodenticides were developed following the discovery that moldy sweet clover poisoning in cattle, a hemorrhagic syndrome, is caused by the fungal metabolite dicoumarol. The primary mechanism of action of FGARs is through inhibition of the synthesis of vitamin K–dependent clotting factors in the liver; however, many of the compounds in this group also have ancillary effects based on their active metabolites. Although marketing of these products has waned with

the introduction of SGARs to the market, FGAR rodenticides are still commonly used.

Warfarin—Warfarin was the first marketed anticoagulant rodenticide and remains a mainstay in the US market for rodent control, with 23 products currently registered with the EPA.[6] Warfarin is currently available in a variety of concentrated forms for home (0.5%) and commercial use (100%) as well as solid forms (0.005% to 0.25%) and is sold under brand names such as Prolin, Kaput, and Rodex. In addition to its inhibition of vitamin K–dependent clotting factors in the liver, warfarin is metabolized to 2 active metabolites that cause direct capillary damage (4-hydroxycoumarin and benzalacetone).[2] Warfarin residues are of concern to humans because many people with cardiovascular disease are prescribed anticoagulants and additional intake of warfarin through contaminated tissues increases the risk of toxicosis. Given the widespread use of warfarin as a therapeutic in human medicine, there are plentiful data on the effects and adverse events of this compound in humans. Warfarin is teratogenic in humans, with the greatest risk of teratogenicity at 6 to 9 weeks' gestation.[7] Teratogenic syndromes secondary to warfarin consumption have been reported in humans, rodents, and frogs.[7] These syndromes consist of nasal hypoplasia, chondrodysplasia punctate, optic atrophy, and neurotoxicity.[7] There are limited published data on the environmental fate and degradation of warfarin, suggesting that degradation of warfarin in soil is primarily through microbial means.[8]

There are a small number of studies examining the effects of warfarin in food animals. Pigs in general have a relatively low tolerance for warfarin, with a reported single dose oral LD_{50} of 1 to 15 mg/kg and a repeated dose LD_{50} of 0.05 mg/kg for 7 days.[9] In micromini pigs administered 0.2 mg/kg warfarin, IV, the plasma half-life was reported to be between 16 to 17 hours **(Table 2)**.[10]

In a small pilot study[11] of 4 cattle administered warfarin at a dose of 5 mg/kg, IM, warfarin residues could still be detected in milk 16 days after treatment. Residues were also detectable in the liver, kidney, spleen, pancreas, lung, and muscle tissue 16 days after treatment.[11] First-generation anticoagulant rodenticides, such as warfarin, are poorly degraded by the ruminal microflora of sheep, and no decrease in warfarin concentration was noted following a 12-hour incubation period in ovine rumen fluid.[12] In sheep administered warfarin at a dose of 5 mg/kg IV or intraruminally, bioavailability was 79.3%, with a terminal plasma half-life of 9.49 hours (Table 2).[12] The pharmacokinetics of warfarin administered at lower doses remain unknown in ruminants.

Poultry species are relatively resistant to warfarin toxicosis, with a reported LD_{50} as high as 942 mg/kg in chickens and 620 mg/kg in mallard ducks.[13] In chickens, warfarin has a longer plasma half-life than in other species, with plasma half-lives of up to 34 hours reported following a single oral dose of 1.5 mg/kg (Table 2).[14] Data for warfarin disposition in eggs are limited. Following oral exposures of 10 or 30 mg/kg for 5 days in chickens, warfarin residues were present in the egg whites for up to 5 days and in the yolk for > 14 days after dosing.[15] Use of this information to calculate an elimination half-life for repeated dosing of 10 mg/kg reveals an elimination half-life of 50 hours for egg whites.

Historically, FARAD has been unable to provide a data-driven recommended WDI for warfarin on the basis of the scant pharmacokinetic data available in swine, poultry, and ruminants. There are limited egg-specific pharmacokinetic data, and therefore veterinarians are advised to contact FARAD for scientifically based egg WDIs following exposure of commercial or backyard poultry to warfarin. Given the scant available plasma pharmacokinetic data and no published tissue pharmacokinetic data, we recommend that veterinarians presented with pigs and ruminants exposed to warfarin contact FARAD for case-specific WDIs.

Coumatetralyl—Coumatetralyl, when placed in the continuum of FGARs, is considered more potent than warfarin and pindone but less potent than the SGARs brodifacoum, flocoumafen, or bromadiolone. Similar to other FGARs, coumatetralyl requires several consecutive days of feeding to be effective. Although labels for this product exist in other countries, there are currently no EPA-approved coumatetralyl products in the US.[6] There are scant pharmacokinetic data available in red deer where administration of a single oral dose of 8.5 mg/kg resulted in a mean hepatic elimination half-life of 18.9 days (range, 14.5 to 27.3 days; Table 2).[16] Hepatic concentrations were below the limit of detection (0.1 µg/g) by 85 days after dosing.[16] Although coumatetralyl toxicosis is unlikely to occur in the US owing to the lack of EPA-registered products, there is moderate scientific evidence for the formulation of a meat WDI in cervids and no scientific evidence for formulating a WDI recommendation in any other species.

Indanediones

Pindone—Pindone, an indanedione, works through interference with vitamin K–dependent clotting factor synthesis by the liver. It also has insecticidal and fungicidal activity via an unknown mechanism.[17] Because pindone is considered less potent than the newer drugs diphacinone and chlorophacinone, it can be considered obsolete, and there are currently no active EPA registrations for this compound.[6] However, given that there are a number of studies that examine the persistence of pindone in sheep, examination of the pharmacokinetics of pindone in this species is important for generating WDI recommendations for other indanediones in small ruminants. The LD_{50} for a variety of species is high because of the low potency of pindone. In rabbits, the most sensitive species reported, the LD_{50} is 25 mg/kg, whereas the LD_{50} is > 75 mg/kg in sheep, dogs, and possums.[9]

In sheep, oral administration of pindone at doses of 2 to 10 mg/kg resulted in a plasma half-life of 96 to 120 hours.[18] Following oral administration of pin-

done at a dose of 10 mg/kg, liver and fat residues persisted for 8 days and were below the limit of detection (0.09 ug/g) at 16 days.[19] Following oral administration of a 3-day declining dose regimen (10 mg/kg, 3 mg/kg, and 2 mg/kg), pindone residues were detected in the liver at 22 days.[18] Although toxicosis is unlikely to occur in the US because of the lack of active EPA-registered products, there is moderate scientific evidence for the formulation of a meat WDI in sheep and no scientific evidence for formulating a WDI in any other species.

Diphacinone—Diphacinone is more toxic than warfarin and pindone but less toxic than the typical SGARs, leading to some confusion as to whether it should be classified as an FGAR or SGAR. Diphacinone has been used as a broad-scale method for controlling rodent field populations owing to its shorter persistence in rats and lower risk for acute toxicosis in nontarget species relative to the SGARs.[20] There are 144 combined active EPA registrations for diphacinone and its sodium salt under various brand names, including Tomcat, Ramik, Kaput, and D-Con, with a labeled 0.106% liquid concentrate and a variety of solid forms with diphacinone concentrations ranging from 0.01% to 99%.[6] The reported LD_{50} in swine is > 150 mg/kg, which is much greater than that in dogs (3 to 7.5 mg/kg) and Norway rats (1.93 to 43.3 mg/kg).[20] Although there are minimal LD_{50} data for poultry, mallard ducks appear to be very resistant to diphacinone, with an LD_{50} of 3,158 mg/kg.[9] Diphacinone is one of the few anticoagulant rodenticides with published environmental kinetics, with a 30-day half-life under aerobic conditions in soil and a 60-day half-life under anaerobic conditions in soil.[17]

In swine, the reported mean hepatic elimination half-life of diphacinone (1.5 mg/kg, PO) is 12.4 days (range, 8.1 to 21.0 days; Table 2), with all samples below the limit of detection (0.05 ug/g) by 43 days after dosing.[16] When the dose was escalated to 12.5 mg/kg, the mean hepatic elimination half-life was 14.12 days. Utilizing these data, researchers determined that it would take 104 days for hepatic concentrations to decline below the limit of detection (0.02 ug/g).[20] Following the oral administration of same single dose (12.5 mg/kg), muscle concentrations were below the limit of detection but hepatic concentrations were still present above the limit of detection at 15 days after dosing.[20] To determine whether food preparation technique has an impact on tissue residues, swine were administered diphacinone (3.5 to 7.4 mg/kg) and tissues were analyzed 3 days posttreatment following a variety of preparation techniques (raw, baking, boiling, and roasting).[21] Both liver and muscle contained diphacinone residues following all cooking methods, indicating that anticoagulant rodenticide residues survive various cooking processes. This finding has broad implications for the persistence of tissue residues of rodenticides in the harvest of both domestic and feral swine.

Mean hepatic elimination half-life of diphacinone was 5.3 days (range, 3.4 to 12.4 days; Table 2) for deer given 1.5 mg of diphacinone/kg, PO, once, and all hepatic samples were below the limit of detection (0.1 µg/g) by 29 days.[16] However, it is important to note that hepatic elimination was nonlinear, and there was an increase in hepatic diphacinone concentrations between days 5 and 12 for one deer and between days 1 and 5 for another.

Cattle have longer hepatic persistence of diphacinone, compared with other ungulates, including swine and red-tailed deer.[16] In an early study[22] of diphacinone injected intraruminally at 1 mg/kg, liver residue concentrations were nearly identical at 30, 60, and 90 days after injection. In cattle orally administered 1.5 mg of diphacinone/kg, the mean terminal hepatic elimination half-life was 25.2 days for heifers and 35.4 days for steers, with the longest reported elimination half-life of 49.5 days (Table 2).[16] Based on these data, complete depletion for diphacinone in cattle exposed to 1.5 mg/kg orally is estimated to be 495 days. The metabolism and distribution of diphacinone are markedly different in cattle, compared with deer and swine, which may have broader implications for attempting to extrapolate WDIs for accidental exposure in cattle using pharmacokinetic data from other species.[16] In rats and pigs, hepatic elimination of anticoagulants occurs in a biphasic pattern, with a steep initial elimination phase followed by a more gradual terminal elimination phase. Cattle demonstrated a higher maximum plasma concentration than swine or deer that were given the same oral dose (1.5 mg of diphacinone/kg), and their hepatic elimination patterns suggest that there is a greater degree of enterohepatic circulation of diphacinone in cattle than in pigs or deer, resulting in prolonged hepatic residues.[16] There are scant milk elimination data for diphacinone in cattle. In a small study of 3 cattle administered 2.75 mg of diphenadione (diphacinone)/kg, milk residues were below the limit of detection of 3 ppb at 72 hours posttreatment.[23] For 3 cattle administered 1 mg/kg diphenadione, no milk residues were above the limit of detection at any time point.[23]

Given the large number of active EPA registrations for diphacinone, there is a great potential for exposure of food animals. The FARAD has received calls for the formulation of WDIs in beef cattle, swine, and poultry. There are robust specific tissue elimination data for this compound that can be used to provide an evidence-based WDI for known or estimated exposures in cattle,[16] cervids,[16] and swine.[16,20,21] Similarly, extrapolations from cattle data could be used to provide an estimated meat WDI for small ruminants. Unfortunately, there are no tissue, plasma, or egg data to support the provision of evidence-based WDIs in avian species. Therefore, veterinarians are advised to contact FARAD with any cases of food animal exposure to diphacinone for the formulation of a WDI.

Chlorophacinone—Similar to diphacinone, chlorophacinone also faces confusion regarding its classification as an FGAR or SGAR. There are currently 50 active EPA registrations for chlorophacinone under such brands as Rozol, JT Eaton, and Attax.[6] Chloro-

phacinone is available as a powder, pellets, and soft baits with concentrations ranging from 0.005% to 2% in commercial products as well as a 98.9% technical-grade product. Unfortunately, the literature contains only limited toxicokinetic data for chlorophacinone. The only food animals with reported LD_{50} data include rabbits (50 mg/kg) and ducks (100 mg/kg).[24] Chlorophacinone poisoning has been documented as the cause of fatal hemorrhage in lambs.[24] In sheep administered 1 mg/kg, IV and intraruminally, chlorophacinone had a 92.2% bioavailability, with a terminal plasma half-life of 30.13 hours (Table 2).[12] It was also noted that chlorophacinone is poorly, if at all, degraded by the ruminal microflora of sheep. Following a 12-hour incubation period in rumen fluid, there was a minimal decrease in chlorophacinone concentrations.[12] Although the active EPA registrations for chlorophacinone make the potential for farm use and exposure to food animals higher than other rodenticides, FARAD has not received any submissions related to food animal exposure to this product. Also, although there are limited plasma data in sheep suggesting a long plasma elimination half-life, there are no specific tissue data to support the provision of an evidence-based WDI for this compound. Therefore, there is very poor scientific evidence for the formulation of a WDI in any species.

Second-Generation Anticoagulant Rodenticides

Second-generation anticoagulant rodenticides are frequently referred to as superwarfarin compounds because they also interfere with vitamin K synthesis, but they exhibit greater potency than FGARs. Second-generation anticoagulant rodenticides largely act by antagonizing vitamin K1 epoxide reductase, thereby depleting vitamin K–dependent clotting factors and are more extensively bound to plasma and tissue proteins than are FGARs, resulting in prolonged elimination.[1,2] They typically undergo extensive enterohepatic recirculation prior to biliary excretion and subsequent fecal excretion of the unbound compound, leading to prolonged exposure in affected animals. Second-generation compounds have increased affinity for vitamin K 2,3 epoxide reductase and vitamin K quinone reductase, leading to accumulation in tissues containing these reductases such as the liver, pancreas, and kidneys.[25] Due to this accumulation effect, these tissues should be considered the target organs for determining the elimination of SGARs and subsequent safety for human consumption. This group contains some of the most used products on the market and represents the greatest share of submissions to FARAD for food animal exposures to rodenticides (Table 1). To reduce the risk of exposure of children and wildlife to rodenticides, the EPA developed a series of measures in its 2008 Risk Mitigation Decision. These measures included restrictions on package size, use, and sale or distribution of products that contain the SGARs brodifacoum, bromadiolone, difenacoum, difethialone. Although this has led to decreased availability and use of these products in consumer home environments, the use of SGARs for rodent control is still frequent in farm and agricultural settings.

Brodifacoum—Brodifacoum is one of the more common rodenticides for which FARAD receives queries for WDIs following accidental exposure of food animals, with 23 submissions involving various species. There are currently 38 active EPA registrations for brodifacoum, marketed under such brands as Havoc, Talon, Final, Syngenta, BDF, and Jaguar.[6] Brodifacoum is available in a variety of forms and concentrations, ranging from 0.0025% to 0.005% solid, 0.25% concentrates, and 90% to 98% technical-grade products. Brodifacoum is readily absorbed following gastrointestinal or dermal exposure in a variety of mammals. There are multiple reports of the toxicokinetics of brodifacoum in veterinary species. The LD_{50} in poultry varies by species, ranging from < 1 mg/kg (Canadian geese) to up to > 20 mg/kg (paradise shelducks),[26] with chickens having an LD_{50} of 3.15 to 20 mg/kg.[5,13] The reported LD_{50} for swine is 0.1 to 10 mg/kg.[5,9] One potential route of exposure in swine, either domestic or wild, is via the scavenging of rodent carcasses, because rodents that have died up to 1 year following sublethal exposure have been reported to still carry active drug residues.[26] In sheep, the LD_{50} has been reported to be between 5 and 25 mg/kg.[5] Sublethal exposure of brodifacoum in sheep may cause reproductive effects, including abortion and reduced lambing rates.[27] Brodifacoum is very insoluble in water and does not appear to be mobile in soil, with a soil half-life of 12 to 25 weeks following microbial degradation.[28] Although the risk of exposure due to runoff has historically been reported to be minimal, the lethal concentration for 50% of the population (LC_{50}) for rainbow trout in water is 0.04 to 0.155 mg/L.[29] The reported LD_{50} for red-toothed triggerfish is 36 to 48 mg/kg and 50 to 75 mg/kg for black triggerfish.[30] Brodifacoum also exhibits high bioaccumulation potential in fish and has been detected in fish from wastewater treatment plants.[29]

In sheep administered a single oral dose (either 0.2 or 2.0 mg/kg) of brodifacoum, hepatic residues persisted for > 128 days.[31] At 128 days after dosing, liver residues were 1.07 mg/kg for the 2.0-mg/kg treatment group and 0.64 mg/kg for the 0.2-mg/kg treatment group. Extrapolations from these data suggest that hepatic residues would persist for upwards of 250 days in both groups. Residue concentrations fell below detectable limits in muscle at 32 days for the 0.2-mg/kg treatment group and at 64 days for the 2.0-mg/kg treatment group.[31] Pigs had liver brodifacoum residues of approximately 1 mg/kg 5 days after consuming contaminated possum tissues and therefore are at risk of secondary brodifacoum poisoning.[26] From a food safety perspective, this would mean that for a healthy 60-kg adult human not on anticoagulant therapy to consume an LD_{50} dose (< 1 mg/kg) of brodifacoum, the person would need to eat approximately 15 kg of a liver containing 1 mg of brodifacoum/kg to be poisoned.[26]

In chickens, following a single oral exposure of 0.5 mg of brodifacoum/kg, liver residues remained constant for 14 days after dosing.[32] However, brodifacoum was found to have an average half-life of 5.3 days in muscle, 2.79 days in fat, 3.17 days in ovaries, and 1.14 days in plasma (Table 2).[32] Brodifacoum concentrations in eggs were highest (0.035 µg/g) 14 days after dosing.[32] Because there were rising concentrations over the entire postdosing sampling period, we do not have any egg elimination data and extremely prolonged discard times were necessary for brodifacoum depletion.

Given the large number of active EPA registrations for brodifacoum, the potential for farm use and exposure in food animals is high, which is reflected in the number of queries submitted to FARAD for this product. Currently, there are no hepatic or plasma elimination kinetic data for brodifacoum with which to determine a scientific-based WDI for swine. Veterinarians are encouraged to submit a request to FARAD in cases of swine exposure should new data or registrations become available. In poultry, there are no specific hepatic elimination data to determine a scientific-based WDI. However, the hepatic elimination half-life is > 14 days in poultry. The muscle tissue half-life of 5.3 days may be used to formulate a WDI for personal consumption of poultry, provided organs are discarded. Due to the rising brodifacoum concentrations in eggs 14 days following administration of a single oral dose, there are insufficient data to suggest a scientific-based egg discard interval. In ruminants, hepatic brodifacoum residues are likely to persist for up to 250 days following a single oral exposure of up to 2 mg/kg. There are currently no data on milk elimination of brodifacoum. Therefore, overall, there is limited scientific evidence to provide an evidence-based meat WDI for personal consumption of poultry, strong scientific evidence for sheep, and no evidence to support a scientific-based WDI for milk in any species or eggs in poultry.

Bromadiolone—Bromadiolone is a commonly used SGAR with 67 active EPA registrations under such brands as Hawk, Kaput, Maki, Brigand, Resolv, and Boothill.[6] Due to the widespread nature of its use, it is responsible for the largest number (n = 24) of FARAD submissions for food animal rodenticide exposure. Despite being an SGAR, bromadiolone's extensive use has led to the development of resistance in rodents, particularly field populations. The LD_{50} for bromadiolone in chickens following long-term use has been reported to be 5.0 mg/kg, which is higher than that reported for swine (0.5 to 3.0 mg/kg).[9] Although bromadiolone is fairly water insoluble and therefore waterway contamination is unlikely, it is highly bound to soil, leading to slow degradation (soil half-life, 1.8 to 23 days) and environmental persistence where used.[9,33] Hepatic bromadiolone residues have been reported in fish in proximity to wastewater treatment plants, which may be secondary to rodent control in sewer systems or stormwater overflow structures; therefore, it is a risk to aquatic species.[29] In a study[7] comparing the teratogenic potential of warfarin and bromadiolone in rats, bromadiolone was found to have fewer teratogenic properties than warfarin.

The toxicokinetics of bromadiolone are similar to brodifacoum in the reported species. Bromadiolone is poorly degraded by the ruminal microflora of sheep. Following a 12-hour incubation period in rumen fluid, there was a minimal decrease in bromadiolone concentration.[12] In sheep administered 1 mg/kg, IV and intraruminally, bromadiolone had 88% bioavailability and a terminal plasma half-life of 49.5 hours (Table 2).[12] In sheep receiving 2 mg/kg PO, bromadiolone was detected in the liver for 256 days.[19]

In swine, following a single oral administration of 0.5 mg of bromadiolone/kg, the mean hepatic bromadiolone concentration was 213 µg/kg at 9 weeks after dosing.[34,35] Extrapolating from these data, the researchers proposed a 176-week (1,232-day) WDI following a single oral dose of 0.5 mg/kg in swine.[35] By use of the reported data from that study,[35] a hepatic half-life of 908 to 1,091 hours (approx range, 38 to 45 days; Table 2) could be estimated. Following a single oral administration of 0.05 mg/kg, the mean hepatic bromadiolone concentration was 51.8 ug/kg at 6 weeks after dosing.[34] Skin, fat, feces, and plasma concentrations of bromadiolone were all below the limit of detection at 6 weeks after dosing.[34] Based on these data, the researchers proposed an 83-week (581-day) WDI following a single 0.05 mg/kg oral exposure in swine.[35] Utilizing hepatic elimination kinetics data from that study,[34] a hepatic half-life of 718 hours (approx 30 days; Table 2) could be calculated for a single 0.05 mg/kg oral exposure in swine.

In chickens, there are a limited number of studies exploring egg residues following bromadiolone exposure. Following a single oral dose of 10 mg/kg, bromadiolone was detected in egg yolks up to 7 days after exposure.[36,37] Following a single oral dose of 60 mg/kg, bromadiolone was detected in egg yolks up to 9 days after exposure.[36,37] In hens fed a range of doses from 1.3 to 19.2 mg of bromadiolone/kg, no egg residues were detected out to 22 days after dosing. However, it is important to note that the hens ceased laying from days 5 to 11, presumably owing to the bromadiolone toxicosis, which may have indicated that eggs in the formative stages had been exposed.[38] Although chickens lay eggs every 24 to 48 hours following a rapid maturation phase, egg precursor components may be present for months prior to maturation.[39] Therefore, a decreased frequency between successive lays may lead to an increase in exposure of the eggs to a chemical substance and subsequent heightened risk of residues.

Based on the many active EPA registrations and many queries submitted to FARAD for bromadiolone exposure in food animals, there is a high risk of exposure from the farm environment. There is limited scientific evidence to provide an evidence-based meat WDI for personal consumption of meat from small ruminants or eggs from poultry. Strong scientific evidence is available for the formulation of an evidence-based meat WDI in swine. There is no evidence to support a scientific-based WDI for milk in any species. However, from examining the above data, bro-

madiolone is a very persistent toxicant, suggesting that caution be used to ensure that exposed animals do not enter the food supply.

Difethialone—Although there are 31 active EPA registrations and a variety of products available for difethialone,[6] there have only been 3 submissions for food animal exposure to FARAD. Difethialone is available in a variety of forms ranging from 0.0025% solid to 98.6% technical-grade under brands such as Generation, Enforcer, FirstStrike, and Hombre. There is evidence that difethialone can be an environmental contaminant, with residues detected in the livers of fish from wastewater treatment plants.[29] The only kinetic data available for difethialone are in mice. In mice administered 0.65 mg of difethialone/kg, the plasma elimination half-life was 38.9 days and the hepatic elimination half-life was 28.5 days, suggesting an extended persistence of the drug in tissues.[40] Therefore, there is currently no scientific evidence to support an evidence-based WDI for any product in any food animal species.

Flocoumafen—Flocoumafen is a 4-hydroxycoumarin derivative of the naturally occurring compound coumarin. The compound has no active EPA registrations.[6] Lethality occurs once complete saturation of hepatic binding sites for the compound occurs and therefore is extremely species specific.[41] Rats poorly metabolize this compound, so saturation occurs quickly, whereas quail extensively metabolize flocoumafen, leading to lower toxicity.[42] There are species differences in small ruminants in terms of response to flocoumafen. Sheep have an LD_{50} of > 5.0 mg/kg, whereas goats have an LD_{50} of > 10.0 mg/kg.[17] Pigs and chickens appear to be fairly resistant to flocoumafen, with an oral LD_{50} of 60.0 mg/kg for pigs and > 100 mg/kg for chickens.[9]

In poultry, groups of layer chickens were administered flocoumafen at 0, 1.5, 5.0, 15.0, or 50.0 mg/kg in feed for 5 days.[41] At 15 days following the treatment period, all surviving birds were euthanized. Although liver residues were detected in all chickens 15 days after treatment, muscle, fat, and skin residues were present only in the 5-, 15-, and 50-mg/kg groups.[41] There was a 30%, 40%, and 80% mortality rate prior to study completion for the 5-, 15-, and 50-mg/kg groups, respectively.[41] Flocoumafen residues persisted in egg yolks over the entire 19-day study interval for layers administered 1 or 4 mg of flocoumafen/kg/d for 5 consecutive days.[41] In quail, hepatic residues were present for 112 days following a single oral dose of 14 mg of flocoumafen/kg, with a hepatic elimination half-life of > 100 days.[42] In sheep receiving 0.2 mg of flocoumafen/kg, hepatic residues were present for 128 days after dosing.[19] There is limited scientific evidence to support an evidence-based meat WDI for sheep and quail. There is extremely limited evidence to support an egg or meat WDI for exposed chickens. No evidence is available to support a scientific-based WDI for milk in any species or meat in other food animal species.

Difenacoum—Difenacoum is an SGAR with 1 active EPA registration and is available under the brand name Monark in a 0.005% solid form.[6] Despite the active registration, there have been no FARAD submissions for any food animal species (Table 1). The LD_{50} is reported to be 80 mg/kg in swine, 50 mg/kg in chickens, and 100 mg/kg in sheep.[5] Rabbits are particularly susceptible to difenacoum, with an LD_{50} of 2.0 mg/kg.[5] There is some evidence of environmental contamination because difenacoum has been detected in the livers of fish from wastewater treatment facilities.[29] Unfortunately, there are extremely limited toxicokinetic data available for difenacoum in veterinary species, with the only data available in mice. In mice administered 0.4 mg of difenacoum/kg, the plasma elimination half-life was 20.4 days and the hepatic elimination half-life was 61.8 days, suggesting an extended persistence of the drug in tissues.[40] Therefore, there is no scientific evidence to support an evidence-based meat WDI in food animal species that is not extrapolated from mouse data.

Nonanticoagulant Rodenticides

There is a variety of rodenticides that do not exert their effects via disruption of the coagulation cascade. This broad variety of compounds is included under the nonanticoagulant rodenticide category and represents the greatest number of EPA registrations and most commonly used rodenticides.

Bromethalin

Bromethalin carries the largest number of EPA registrations of any rodenticide, with 190 active registrations under a variety of brands such as Victor, Tomcat, Rampage, Surekill, Assault, and many others.[6] Bromethalin is responsible for 17 FARAD case submissions between 1999 and 2021 (Table 1). It is available as a 0.01% and 0.025% solid, 2% concentrate, and 98.4% technical-grade form. Bromethalin's mechanism of action is to inhibit oxidative phosphorylation in the affected animal's mitochondria. Bromethalin is rapidly absorbed from the intestines and transported to the liver, where it is metabolized to its more potent and active metabolite, desmethyl bromethalin. Desmethyl bromethalin is highly lipid soluble and therefore penetrates the CNS where it inhibits oxidative phosphorylation, leading to cerebral edema, increased intracranial pressure, and ultimately diffuse spongiosis of the white matter.[43] Due to the lipophilic nature of bromethalin and its mechanism of action, the CNS and fat are considered sites of accumulation and therefore would be the target tissues for testing. Bromethalin undergoes enterohepatic recycling, leading to a prolonged duration of action. Clinical signs are dose-dependent and appear between 4 hours and 7 days after ingestion.[43] Methods have been recently published for the characterization of bromethalin and its metabolites by gas chromatography–tandem mass spectrometry.[44] The LD_{50} is dependent on N-demethylase activity because lower N-demethylase activity leads to less production of the more toxic metabolite, desmeth-

yl bromethalin.[45] Following oral exposure, the LD_{50} is 1,000 mg/kg for guinea pigs (animals with low N-demethylase activity), 13 mg/kg for rabbits, 3.65 mg/kg for dogs, and 0.54 mg/kg for cats.[46] Swine are extremely sensitive to bromethalin toxicosis, with an LD_{50} of 0.25 mg/kg.[47] Trout have an LC_{50} of 0.033 to 0.080 mg/kg, and mallard ducks have an LD_{50} in feed of 620 mg/kg.[48]

Bromethalin is considered carcinogenic by the EPA and World Health Organization, raising concerns for any bromethalin residues in the tissues of food animals.[47] Despite a large number of active EPA registrations and a substantial number of submissions received by FARAD, toxicokinetic data for bromethalin are lacking. There are no toxicokinetic studies for bromethalin or its metabolites in any food animal species, making formulation of an evidence-based WDI problematic. The only kinetic data available are in Fischer 344 rats that were administered radio-labeled bromethalin at a dose of 1 mg/kg, revealing a terminal plasma elimination half-life of 5.6 days.[49] Therefore, there is no evidence for the provision of evidence-based meat, milk, or egg WDI in any food animal species. Given the carcinogenic potential of bromethalin, it is recommended that animals exposed to bromethalin never enter the food chain.

Cholecalciferol

Cholecalciferol (vitamin D_3) is required by the body, but overdoses can lead to dystrophic mineralization, acute renal failure, and gastrointestinal, muscular, and cardiovascular complications.[47] The mechanism of action of cholecalciferol toxicosis is through its active metabolite, calcitriol. Cholecalciferol is metabolized by the liver to calcifediol, which is then metabolized by the kidney to calcitriol, the active metabolite. The metabolites work to increase serum calcium and phosphorus concentrations by increasing intestinal calcium absorption, stimulating calcium and phosphorus release from bone, and enhancing renal tubular reabsorption of calcium.[46] A high concentration of intracellular calcium is an important factor in the development of life-threatening ventricular arrhythmias (tachycardia and fibrillation) and increases the prevalence of atrial arrhythmias such as fibrillation and flutter.[50] The most common clinical signs of cholecalciferol ingestion in horses,[51] dogs,[52] and cats[52] include anorexia, weakness, polyuria, and polydipsia; however, cardiac arrhythmia and myocardial mineralization have been described in cases of severe toxicosis.

There are currently 17 active EPA registrations for cholecalciferol products as a 0.075% solid.[6] Despite the number of EPA registrations, there have been no FARAD submissions for food animal exposure to cholecalciferol rodenticides (Table 1). Clinical signs of toxicosis can be seen at doses as low as 0.5 mg/kg in dogs, which means that a 23-kg dog would only need to ingest 14.2 g of 0.075% cholecalciferol bait.[45] The oral LD_{50} for cholecalciferol in rodents is quite high at 43 mg/kg. Avian species appear to be relatively resistant to cholecalciferol toxicosis, with an LD_{50} > 2,000 mg/kg in mallard ducks and a dietary LC_{50} of 2,000 ppm in bobwhite quail.[47] However, isolated cases of cholecalciferol toxicosis in wild birds have been reported in areas where cholecalciferol is used as rodent bait.[53] Unfortunately, there are no toxicokinetic data available for cholecalciferol in food animals. However, as a naturally occurring product, the risk to human health following consumption of food products containing cholecalciferol residues is likely minimal. We encourage veterinarians to contact FARAD for WDI recommendations for animals exposed to cholecalciferol rodenticides.

Zinc phosphide

Zinc phosphide is highly toxic to humans and is listed in toxicity category I (the highest category) for acute effects via oral or inhalation routes.[54] With 102 active EPA registrations and availability in a variety of solid (2%) and concentrated (63.2% to 82%) forms, zinc phosphide contamination has been reported in a variety of veterinary species.[6] When zinc phosphide is ingested, contact with stomach acids and water leads to the production of highly toxic phosphine. Animals may also be exposed through the consumption of feed or forage that has been fumigated with phosphine or aluminum phosphine.[47] Humans may be exposed to toxic phosphine gas from affected animals through regurgitation, eructation, or release of phosphine gas during decontamination or postmortem examination.[55] Human cases of phosphine poisoning have been reported following treatment of animals affected by zinc phosphide rodenticides.[55] Due to substantial human health concerns, any veterinarian examining, treating, or performing a postmortem examination on animals suspected of zinc phosphide poisoning should adhere to appropriate precautionary measures including performing such procedures in a well-ventilated space.

In sheep, the oral LD_{50} ranges from 60 to 70 mg/kg.[47] In birds, the LD_{50} ranges from 7.5 to 12 mg/kg in geese, is 25 mg/kg in chickens, and is 67.4 mg/kg in mallard ducks.[54] Unfortunately, there are no kinetic data for zinc phosphide in any species. Therefore, there is no evidence for the provision of an evidence-based meat, milk, or egg WDI in any food animal species. Given the extremely toxic nature of zinc phosphide to human health, we recommend that animals exposed to zinc phosphide never enter the food chain.

Strychnine

Strychnine is an extremely toxic alkaloid that inhibits glycine. Because glycine is an inhibitory transmitter to motor and interneurons in the spinal cord, it leads to reflex excitability of muscular fibers. This ultimately causes convulsion, seizure, suffocation, and death in affected animals. There are 21 active EPA registrations for strychnine, and it is available as a 0.5% commercial solid as well as 3.2% and 98.4% restricted-use technical-grade products.[6] Like zinc phosphide, strychnine is highly toxic to humans and is labeled as a toxicity category I substance for oral, ocular, and inhalation effects. The LD_{50} for strychnine is 2.3 mg/kg in rats,

0.6 mg/kg in rabbits, 0.5 mg/kg in dogs, 3 mg/kg in ducks, and 21 mg/kg in pigeons.[47] There is a paucity of toxicokinetic data for strychnine in veterinary species. In humans who have been reported to deliberately self-poison, a plasma elimination half-life of between 10 and 16 hours has been reported in survivors, with rapid urinary elimination.[56] Given the extremely toxic nature of strychnine to human health, we recommend that animals exposed to strychnine never enter the food chain.

Conclusions

There are little data on the absorption, distribution, metabolism, and excretion of rodenticides in common food animal species, with many compounds that are commonly used having very limited reported toxicokinetics. Generally speaking, studies have shown that rodenticides are well absorbed and accumulate most commonly in the liver. There are sparse data available concerning the food safety aspect of food animals exposed to rodenticides. Considering the complexity of different mechanisms of action, potency, and differences in physiology between food animals and common laboratory species, a great deal of research is needed to address this area to further characterize the potential human risk from consuming meat, milk, and eggs from animals that have been exposed to these products. When such exposure occurs, the first step should always be to terminate exposure from the environment and carefully observe animals for adverse signs. Based on the variabilities in elimination half-lives, very slow elimination after exposure, the unknown amount of rodenticide consumed, the zero tolerance for rodenticides in food products, and the unknown rodenticide residue status in food animals exposed to rodenticides, FARAD often has low confidence in the ability to model an evidence-based WDI recommendation for these cases. Furthermore, there is potential for substantial and severe adverse health risks to humans or animals consuming products from food animals exposed to rodenticides, especially in those individuals already on long-term anticoagulant therapy. Because there are potential human health risks, it is often recommended that exposed animals or their products (ie, meat, milk, or eggs) do not enter the food chain and that the animals are disposed of via non–food-rendering routes to ensure that the carcasses are not accessible to dogs, cats, or wildlife. Because the potential to produce violative residues in edible tissues is a function of variable factors such as dose, length of exposure, animal age, or time to market, no simple recommendation on appropriate withdrawal times can be made, and we encourage veterinarians to contact FARAD to formulate a data-driven WDI recommendation following any rodenticide exposure in any food animal species.

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