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The effect of cooking on diphacinone residues related to human consumption of feral pig tissues

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ABSTRACT

We examined feral pig tissues to determine whether the potential hazard of consuming meat from pigs previously exposed to diphacinone rodenticide baits was reduced by cooking. Residue levels were measured in cooked and uncooked tissues of feral pigs exposed to sub-lethal quantities of the anticoagulant rodenticide. Pigs were provided large amounts of baits or untreated food to consume, then euthanized prior to the onset of symptoms indicative of rodenticide poisoning or sickness. For analysis, we grouped pigs into three levels of mean diphacinone consumption: 0, 3.5, and 7.4 mg/kg. None of the pigs displayed obvious signs of toxicity during the study period. The highest concentrations of diphacinone were found in liver tissue. Cooking had little effect on residual diphacinone concentrations. The hazards to humans and pets from meat from feral pigs that consumed the rodenticide diphacinone are not reduced by cooking; consumption of pig meat obtained from areas with active rodent control programs should be avoided.

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1. Introduction

Feral swine or wild pigs (*Sus scrofa*) occur in a variety of habitats throughout the world where they damage agricultural crops, prey on livestock and game species, disrupt native plant communities and damage watersheds, and compete with native species in fragile ecosystems (Graves, 1984; Seward et al., 2004). They act as reservoirs for diseases affecting humans and livestock and, because of increasing contact with humans, are viewed with growing concern (Witmer et al., 2003; Hall et al., 2008). Wolf and Conover (2003) found more than 35 countries concerned with the environmental impacts of feral swine. Moreover, feral swine now occur in nearly half the US states (Witmer et al., 2003) and in some states are managed as game species with substantial income generated by license fees. In many areas of the world, feral swine and related species are also a valued resource for subsistence, recreational, or commercial hunting (Giffin, 1973; Miller, 1993; Clayton et al., 1997; Waithman et al., 1999), often entering the human food chains as a by-product of this extensive hunting effort.

In many of the same habitats occupied by feral swine, rodent control is a high priority for many agricultural producers, land managers engaged in native species conservation, and ecosystem

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restoration projects around the Pacific Basin. In Hawaii, the focal area of our studies, cooperative efforts by state and federal conservation agencies and non-governmental land management and native conservation organizations have resulted in the federal or state registration of aerial broadcast application of rodent bait containing diphacinone as a method to control rat and mouse depredation in native conservation areas (Dunlevy et al., 2000; Eisemann and Swift, 2006). However, feral pigs (*Sus scrofa*) range freely and are hunted as sources of food for subsistence and recreation (Giffin, 1973; Anderson and Stone, 1993) in many of the habitats where diphacinone could potentially be applied, raising the question of the potential human health hazards of diphacinone accumulation in the pig meat. Various operational management programs using bait stations continue (unpublished job progress reports, 1999, 2000, Game surveys and inventories, Hawaii Game Management Program, US Department of Agriculture, Wildlife Services, Honolulu) and there is substantial interest in the efficiencies that could be gained by using aerial baiting methods (Dunlevy et al., 2000). Rodenticide bait pellets can be very attractive to feral pigs. A major concern with the use of aerial broadcast rodenticide application is the effect diphacinone could have on the health of wild pigs accidentally exposed to bait pellets and, subsequently, on the potential health hazards to hunters, their families, and household animals from consuming tissues from exposed pigs. Varying levels of diphacinone residues have been found in liver and muscle tissue samples collected from pigs foraging in the treatment areas reviewed in the ecological and human health hazards assessment conducted by Eisemann and Swift (2006).

Diphacinone (2-diphenylacetyl-1,3-indanedione, CAS Number 82-66-6) is a widely used anticoagulant rodenticide, patented in 1954 and introduced in the United States in 1957 (Gates, 1957), with various registrations for household, industrial, agricultural and conservation rodent control applications (Jackson and Ashton, 1992; Jacobs, 1994). Diphacinone works by inhibiting the vitamin K cycle, reducing the formation of essential blood clotting factors, eventually leading to lethal hemorrhaging (Fisher, 2006). It is one of the “first generation” anticoagulant rodenticides, including chlorophacinone and warfarin, which require multiple feedings for lethal intoxication in most mammals. It has also been used for control of vampire bats by topical application to bats or intra-ruminal injection of cattle (Thompson et al., 1972; Mitchell, 1986), and has been registered as a toxicant for mongoose control related to endangered species protection (Stone et al., 1994). Under a number of other common names (dipaxin, diphenadione, diphacin, diphenacin), it has been used as a human drug as both an anticoagulant and anticonvulsant (Correll et al., 1952; Kamrin, 1997). Diphacinone is rapidly degraded in water by sunlight (Hayes and Laws, 1990). The technical material degrades at 338 °C without boiling (Worthing and Barrie, 1987). When prescribed for humans, the daily therapeutic dose (equal to 0.59 kg of rodenticide bait at the 50 ppm level formulated) far exceeds the potential for accidental human exposure to such bait (Fagerstone, 1997). Diphacinone has largely been supplanted in human drug therapy by warfarin (Hirsch et al., 2001).

Prior laboratory studies have examined acute dietary toxicity and diphacinone residues in domestic pigs. Fletcher offered Ramik Green® pellets, a commercial rodenticide formulation containing 0.005% diphacinone, to domestic pigs at dosages of 0.133 and 0.333 mg/kg body mass per day for 7 consecutive days [Fletcher, 2002, Seven-day range-finding oral toxicity of Ramik Green (0.005% diphacinone) in domestic swine (*Sus scrofa*), unpublished report, Genesis Midwest Laboratories, 38p]. Fisher (2006) evaluated persistence of diphacinone after exposing domestic pigs to single dosages of 2.5 or 12.5 mg diphacinone/kg body mass. In the only study using feral pigs, Keith et al. fed pigs rations of diphacinone-treated corn at a dosage of 0.007 mg diphacinone/kg body mass/day for 2 days (Keith et al., 1990, Field evaluation of 0.0025% Diphacinone bait for mongoose control in Hawaii, US Department of Agriculture, Denver Wildlife Research Center, Denver, Colorado, unpublished report).

Although these earlier studies have provided some information on diphacinone concentrations in raw pig tissue, none have examined the effects of cooking on diphacinone residues. Since diphacinone decomposes at a relatively high temperature, the expectation is that cooking would have minimal effect on residues. However, this issue has continued to be clouded by the local belief that cooking makes pig tissues safe to consume. In this study, we determined diphacinone residue levels in raw and cooked tissues of feral pigs exposed to sub-lethal quantities of diphacinone bait pellets to assess whether cooking reduces the potential toxicological hazards to humans and domestic animals consuming contaminated pig tissue.

2. Methods

2.1. Test subjects and housing

Twelve feral pigs were trapped between March 19, 2008 and April 29, 2008 in Puna and South Hilo districts of Hawaii Island and transported to the National Wildlife Research Center (NWRC) Hawaii Field Station. Eight of the smaller pigs were selected for study (due to reduced handling and restraint required for smaller pigs). Each pig was sexed, weighed, assigned a unique identification number, and marked with an AVID microchip (American Veterinary Identification Devices, Norco, CA). The pigs were housed two at a time in a large, roofed chain-link pen and held in individual cages approximately 1.1 × 1.2 m (0.66 m² of floor space for each animal). Prior to the feeding trials, pigs were fed commercial hog feed (Nutrena Porktrack®

for Swine, 16% protein) and were acclimated to entering a temporary holding pen while the housing cages were cleaned and water and food replenished daily. Fresh water was available *ad libitum* during the entire acclimation period and feeding trials.

2.2. Feeding trials

We randomly assigned a female and a male pig to one of three groups: a control group, a low treatment group, and a high treatment group. During the testing period, treatment pigs were offered a calculated amount of Ramik Green® rodenticide pellets to achieve a high and low dose of diphacinone, either 12.5 and 6.25 mg/kg based on initial animal body mass. However, actual dose was determined by the amount pigs consumed in the various treatment groups. For analysis, we modified the groups, *post hoc*, based on actual bait consumption, resulting in means of 3.5 and 7.4 mg/kg for consumption groups, in addition to the reference group, that were offered commercial hog feed *ad libitum*.

The toxic bait used for this study was commercially available, flavored, one-half inch Ramik Green® pellets manufactured by Hacco Inc., Madison, Wisconsin, containing 0.005% active ingredient diphacinone (50 ppm). An analysis report provided by the manufacturer verified the diphacinone concentration. A representative bait sample was collected upon receipt and later verified by repeated analysis at NWRC laboratories in Fort Collins, Colorado; bait was stored at ambient temperatures until use (TM Primus, Supplement – Determination of diphacinone residues in Ramik Green bait, 2008, unpublished Analytical Services Report, Method 71C – non-validated, National Wildlife Research Center, United States Department of Agriculture, Fort Collins, Colorado).

All food was removed the day before the trials began and pigs were fasted overnight but water remained available *ad libitum*. On the morning of treatment day one, we offered treatment animals the full dosage of Ramik Green® pellets as a no-choice food. On the morning of day two, any bait remaining in the feed trays was weighed and spilled pellets were recovered and counted. The number of spilled pellets was used to estimate spillage mass based on the average pellet mass, determined as 1.2 ± 0.01 g (*n* = 31). On day three, the pigs were euthanized, their end weights recorded, and tissues were harvested for further analyses. We weighed any bait remaining in the feed trays and again counted spilled pellets, thus the pigs had two full days to consume the diphacinone bait material provided.

2.3. Tissue preparation and cooking

Raw liver, fat, and muscle were collected for residue analysis immediately after an animal was euthanized. Muscle and fat are the tissues most likely to be used for human consumption; muscle tissue was taken from the rump, while fat was taken from the abdominal area, under the throat, and from the hind quarters.

One third of the liver, fat, and muscle tissue samples were kept raw and the remaining two-thirds were cooked using methods commonly used by local hunters in Hawaii. The two cooking methods used were boiling and roasting. For boiling, water was heated over a propane burner until it reached a rolling boil and then samples were cooked for approximately 15 min, or until the internal temperature reached 160°F as measured with a meat thermometer. For the roasting method, tissue samples were cooked at 350°F for approximately 40 min in a conventional convection oven or until the internal temperature reached 160°F.

2.4. Diphacinone residue analyses

All tissue samples were weighed and then frozen and placed in individually vacuum sealed bags and sent frozen to the NWRC analytical chemistry laboratories in Fort Collins, Colorado. Approximately 20–25 g of each sample was homogenized in a SPEX liquid nitrogen freezer mill and placed in a bag, vacuum sealed, and maintained at –30 °C until analysis. The extracts were cleaned up with solid phase extraction (SPE) columns using acetonitrile as the extraction solution and analyzed by reverse-phase ion-pairing chromatography (TM Primus, Determination of diphacinone residues in pig samples, 2008, unpublished Analytical Services Reports, Method 143A – Modified and 143A – Modified, supplement, National Wildlife Research Center, United States Department of Agriculture, Fort Collins, Colorado).

2.5. Determination of water content

Preliminary results indicated that diphacinone concentrations in tissue samples increased after both roasting and boiling. We expected that higher concentrations were likely due to water loss during cooking. We analyzed tissue samples were analyzed for water content, by heating one-gram samples of tissue to constant weight in aluminum weigh boats at 102 °C though two heating cycles of four to eight hours each. Because of high variability in sample mass after cooking and in water content (Table 1), we did not attempt to standardize the residues reported.

2.6. Statistical analyses

Statistical analyses on diphacinone concentrations were performed with SAS Version 9.1 (SAS Institute, Cary, North Carolina, 2004). We tested the diphacinone residue concentrations for normality using the Anderson–Darling test and compared the three preparation methods using two-way analysis of variance, followed by Tukey's multiple comparisons test.

3. Results

3.1. Chemical analysis of bait

Two samples of the Ramik Green[®] bait were assayed by NWRC Analytical Chemistry and had a mean concentration of 0.0052%. Quality assurance samples indicated a 100–101% recovery. The bait was deemed well within the acceptable range of concentration (TM Primus, Method 71C, *op cit.*).

3.2. Feeding trials

We had planned on conducting one replicate of each trial but conducted a second with a 12.5 mg/kg diphacinone dose because animals in the first trial had a longer pre-treatment holding period than the rest of the pigs (15 days vs. average of 6 days). However, all pigs at this high treatment level consumed a similar amount of bait in proportion to their own weight.

All pigs were observed consuming the Ramik Green[®] the first day it was offered. No obvious signs of toxicity (external bleeding, lethargy, decreased food intake) were observed. During tissue sample collection, the blood of all pigs clotted immediately, suggesting the animals had not been exposed to a dose high enough to elicit any observable effects. We visually inspected the gastrointestinal tracts and found the contents of the large and small intestines of all pigs fed Ramik Green[®] were clearly green in color, indicating the bait had indeed been consumed.

3.3. Diphacinone consumption

Actual consumption of the active ingredient diphacinone was calculated using amount of Ramik Green[®] consumed and the pig body mass following euthanasia. Daily consumption of diphacinone ranged from 0.4–4.2 mg/kg/day, with an average of 3.7 and 1.7 mg/kg/day for the 12.5 and 6.25 mg/kg treatment levels respectively. One pig offered 6.25 mg/kg of diphacinone consumed less bait in proportion to its size, thus the pigs were grouped by consumption for analysis. The four pigs offered the high diphacinone amount consumed similar amounts of bait. The groups consumed an average total amount of diphacinone of 3.5 and 7.4 mg/kg over

the two day study period, with the highest amount consumed by one animal being 7.7 mg/kg (Table 1).

3.4. Tissue collection and analysis

Because all the pigs used for the trials were sub-adults, it was difficult to collect enough fat tissue to satisfy the minimum 50 g sample size needed for residue analyses. We were able to extract ample fat for raw analysis for all eight pigs but only enough fat to be roasted for two pigs; we were unable to boil fat and recover enough material to be assayed. Approximately 20–25 g of each sample were assayed and analyzed in duplicate. The minimum limit of detection (MLOD) varied by tissue and treatment (Table 1).

3.5. Diphacinone residue levels

Diphacinone concentrations in all control group tissue samples were less than the minimum level of detection (MLOD). Diphacinone concentrations in all treatment group tissues regardless of dosage or cooking method ranged from 0.205 to 0.708 ppm for fat, 0.444–3.212 ppm for liver, and 0.032–0.476 for muscle (Table 1). Diphacinone residue levels increased in parallel to the actual amount of diphacinone consumed. Pigs consuming 3.5 mg/kg had mean uncooked tissue concentrations of 0.223 ppm in fat, 0.660 ppm in liver, and 0.048 ppm in muscle. Pigs consuming 7.4 mg/kg had mean uncooked tissue concentrations of 0.562 ppm in fat, 1.733 ppm in liver, and 0.209 ppm in muscle (Fig. 1). Overall mean concentrations were 0.198 ppm in muscle, 0.437 ppm in fat, and 1.513 ppm in liver. The highest residual concentration of diphacinone in this study was taken from a roasted liver sample (3.650 ppm) while the highest detected in a raw sample was taken from liver (2.690 ppm).

Diphacinone concentration increased in all tissues after cooking. The increase in concentration can be partially attributed to water loss, as all cooked tissues had less water than raw tissue (Table 1). However, the increase in diphacinone concentration (12–67% depending on tissue type) was greater than the difference in water loss (8–16% depending on tissue type) due to cooking. Thus, other mechanisms of mass loss, such as vaporization of volatile compounds, may account for the difference.

Mean residue levels among the different treatments are shown in Table 1 and depicted in Fig. 1. A two-way ANOVA indicated no significant differences among methods (raw, roasted, and boiled) ($F = 0.22$, $df = 2$, $P = 0.8029$) and the interaction of cooking method and tissue type ($F = 0.23$, $df = 3$, $P = 0.8781$). Across the three tissue types, there was a significant difference in the residue level

Table 1
Diphacinone tissue residues in feral pigs fed rodenticide bait containing diphacinone (Ramik Green[®] or commercial hog feed). The minimum limit of detection for diphacinone residues varied by tissue type and treatment ($\bar{x} = 0.027 \pm 0.01$ ppm, $n = 7$).

Cooking method	Tissue	Percent water	MLOD ^a ppm	Mean diphacinone consumption level and residues in tissue		
				0 mg/kg Residue mg/kg (n)	3.5 mg/kg Mean residue mg/kg \pm SE (n)	7.4 mg/kg Mean residue mg/kg \pm SE (n)
Uncooked	Fat	39	0.006	<MLOD (2)	0.223 \pm 0.018 (2)	0.562 \pm 0.55 (4)
	Liver	73	0.073	<MLOD (2)	0.660 \pm 0.216 (2)	1.733 \pm 0.322 (4)
	Muscle	74	0.006	<MLOD (2)	0.048 \pm 0.016 (2)	0.209 \pm 0.063 (4)
Boiled	Fat	na ^b	na	na	na	na
	Liver	67	0.027	<MLOD (2)	0.910 \pm 0.211 (2)	1.940 \pm 0.258 (4)
	Muscle	62	0.020	<MLOD (2)	0.107 \pm 0.009 (2)	0.296 \pm 0.060 (4)
Roasted	Fat	24	na	na	na	0.648 \pm 0.100 (2)
	Liver	64	0.015	<MLOD (2)	1.116 \pm 0.304 (2)	2.335 \pm 0.464 (4)
	Muscle	65	0.041	<MLOD (2)	0.132 \pm 0.016 (2)	0.348 \pm 0.071 (4)

^a MLOD minimum level of detection.

^b Samples were not available to determine residue amounts.

($F = 33.23$, $df = 2$, $P < 0.0001$); liver had higher diphacinone concentrations than fat and muscle.

4. Discussion

Although the daily diphacinone consumption rates for our pigs were higher than the No Observed Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) for rats (0.040 and 0.085 mg/kg/day) even the highest single day consumption (4.2 mg/kg) was well below the oral LD50 of 150 mg/kg in pigs [Hazelton Laboratories, Inc, Falls Church, VA, 1957, Diphacinone (2-diphenylacetyl-1,3-indandione) toxicity to cats, dogs, swine, and poultry, unpublished report]. Shortly after ingestion, pigs can attain high levels of diphacinone without showing signs of poisoning. Fletcher's (*op.cit.*) 0.333 mg/kg/day dose produced obvious signs of poisoning (external bleeding, lethargy, and decreased food intake), followed by recovery within the 21 day study period and two of the twelve pigs in Fisher's (2006) study exhibited lameness when dosed at 0.5 mg/kg/day at days two and six of the 14-day study. Although daily diphacinone consumption in our study (average 1.7 and 3.7 mg/kg/day) was considerably higher than either of these longer term studies; as expected, none of the pigs showed physical symptoms of intoxication and all appeared to be in healthy condition prior to euthanasia. Had our study period been extended, it is likely that we would have observed signs of chronic poisoning, but in practice, hunters or other local people would be less likely to find, much less harvest and consume moribund animals. However, animals that were exhibiting early symptoms of poisoning could be easier to encounter. The two-day exposure period reflected the most probable field exposure scenario for pigs encountering the limited quantities of diphacinone bait used in aerial or ground rodent control operations.

Among recent studies, pigs in our uncooked, 7.4 mg/kg consumption group had the highest mean concentrations of diphacinone residue in fat (0.562 ppm), liver (1.733 ppm), and muscle tissue (0.209 ppm). Keith (*op. cit.*) found mean diphacinone concentrations of 0.42 ppm in liver and less than 0.07 ppm (MLOD) in muscle. When Fletcher (*op. cit.*) exposed his pigs to 0.333 mg/kg/day for 7 days, the pigs had a mean concentration of 0.040 ppm in liver and less than the MLOD in muscle. Fisher (2006) exposed pigs to a single 12.5 mg/kg dose and found diphacinone residues of 0.11 ppm in fat, 0.69 ppm in liver, and 0.05 ppm in muscle. Pitt et al. found the mean concentration of diphacinone

in radio-collared pigs with detectable residue levels to be 1.063 ppm for liver and 0.073 ppm for muscle (Pitt et al., 2006, Diphacinone residues in free-ranging wild pigs following aerial broadcast of rodenticide bait in Hawaiian forests, unpublished report QA-1077, National Wildlife Research Center, Hilo, HI). In comparison, pigs in our study that consumed 3.7 mg/kg/day had mean concentrations of 0.591 ppm in fat, 2.003 ppm in liver, and 0.284 ppm in muscle.

Cooking did not reduce the residual diphacinone concentrations in feral pig tissue. Cooked samples had slightly higher diphacinone concentrations than raw samples even after being corrected for water content, but it is likely the decrease in mass can be attributed to other mechanisms besides water loss. Other volatiles such as fat are readily vaporized or otherwise lost during the roasting and boiling processes.

The levels of diphacinone in pig tissue observed in this study were not high enough to be of clinical risk to humans. The lowest observed effect level based on a change in blood clotting time in rats is 0.2 mg/kg in a single dose and 0.085 mg/kg for 21 days (US EPA, 1998). Based on these effect levels and the maximum concentrations we detected in roasted tissue of 3.65 ppm for liver and 0.541 ppm for muscle, we calculated that a 55 kg person would need to consume either 3.1 kg of liver or 20.3 kg of muscle in a single day, or 1.2 kg/day of liver or 7.9 kg/day of muscle over 14 consecutive days to receive a dose shown to cause detectable changes in blood clotting in rats. Similarly, a comprehensive assessment of hazards from aerial broadcast applications of 0.005% diphacinone baits concluded that the risk to humans consuming pigs harvested in treated areas is very low (Eisemann and Swift, 2006). Our study has established that the hazards associated with possible consumption of pig tissues contaminated by diphacinone rodenticide are not reduced by cooking. However, diphacinone, despite its use as a human drug, can be a potent poison. Application of a wide range of uncertainty factors in risk assessments, typically 10–1000 is common practice when limited data for human exposures are available, although Dourson et al. (1996) believed such universal application was unjustified if data were available to support otherwise. Using a hypothetical safety factor of 1000, extrapolating from a the rat LOEL (acute) to the human NOEL, we note that pharmacological effects might be observed in a 55 kg person consuming as little as 3.1 g of liver or 20 g of muscle in a single day.

Individuals who may be more susceptible to effects of diphacinone such as pregnant women, those with vitamin K deficiency,

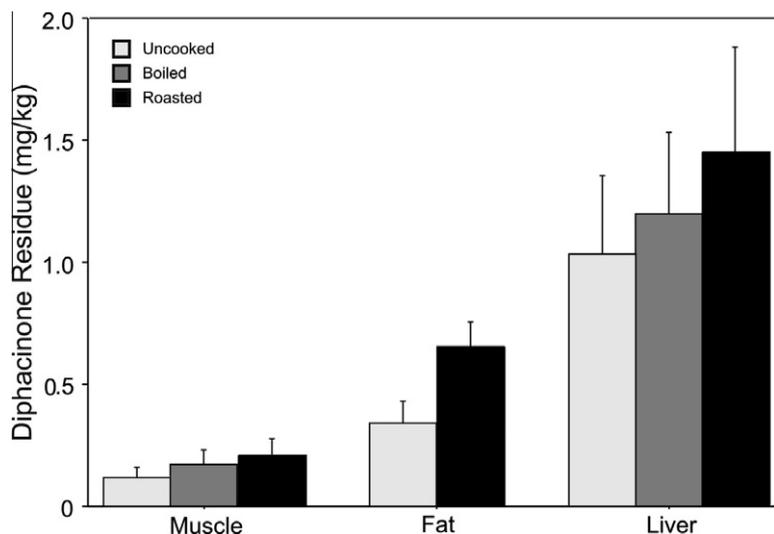


Fig. 1. Residues (overall means and standard errors) of the rodenticide diphacinone in tissues of feral pigs that consumed diphacinone rodent bait. Muscle, fat, and liver were analyzed following cooking by roasting or boiling; uncooked tissues served as reference.

those already taking anticoagulant medications or those with liver disorders, should exercise particular caution and refrain from consuming meat taken from pigs exposed to rodent control operations. Thus, the general public should be notified about potential exposure to rodenticides from aerial broadcast projects and incidents where pigs vulnerable to harvest are potentially exposed to rodenticides from rodent bait stations. Active rodent control programs using diphacinone in areas where pig hunting occurs should consider mitigating potential human exposure risks by signage, public notification, and advice to local physicians on treatment of anticoagulant intoxication.

Concerns have also been voiced about potential risks to hunting dogs or pets from hunters feeding pig carcasses to their dogs (R. Sugihara, US Department of Agriculture, Hilo, Hawaii, personal communication 2008). Three independent reports have listed the diphacinone LD50 for dogs as being 0.88, 3.0–7.5, and 5–15 mg/kg (Erickson and Urban, 2004). Since we found an average diphacinone concentration in liver of 1.73 ppm from pigs consuming the highest dose, even at the lowest reported LD50, a 20-kg dog would have to consume 10.1 kg of liver to receive an LD50 dose. Therefore, the risk of clinical diphacinone intoxication of dogs by this route is very low. Accidental diphacinone poisoning can be treated with vitamin K₁ therapy under a veterinarian's care.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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