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Diphacinone in Pigs: Sublethal Exposure and Residual Persistence in Tissues

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ABSTRACT: Current evaluations of the anticoagulant diphacinone for field control of introduced rodents in New Zealand include risk assessment with respect to non-target mortality, secondary poisoning, and environmental contamination. As non-target wildlife of rodent control operations, feral pigs may be exposed to vertebrate pesticides if they access toxic baits or scavenge the carcasses of poisoned animals. Feral pigs are also a significant resource for recreational hunters who harvest wild pork for food, hence the need to assess the risks of human exposure to diphacinone residues through feral pigs. Pen trials with domestic pigs were used to evaluate the potential for pig mortality through oral exposure to diphacinone and the residual persistence of diphacinone in pig tissues following a sublethal exposure. In the first trial, pigs were offered palatable food containing diphacinone doses of 12.5 mg/kg, 0.25 mg/kg/day for 3 days, or 0.5 mg/kg/day for 5 days. Significant elevations in coagulation time tests were measured 2 days after dosing, but these had returned to baseline values by 7 days. Two of the dosed pigs were euthanased due to lameness, which was accompanied by elevated prothrombin times and severe hemorrhage in a leg joint. In the second trial, pigs were dosed with 12.5 mg/kg diphacinone and then euthanased in groups for tissue sampling at Days 1, 4, and 10. Liver, muscle, and fat samples were analysed for diphacinone residues using an HPLC method. Data fitted to an exponential decay model estimated the hepatic elimination half-life as between 5.43 days (overall) and 14.12 days (terminal phase only). Half-lives of diphacinone in pig muscle and fat were 4.48 and 2.29 days respectively. A conservative withholding period of approximately 160 days is suggested before feral pigs should be taken for human consumption from areas where diphacinone baits have been used. This would minimize the likelihood of detectable diphacinone residues ($\geq 0.02 \mu\text{g/g}$) occurring in wild pork.

KEY WORDS: anticoagulant, coagulation time, diphacinone, half-life, liver, meat, pig, residue, *Sus scrofa*

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INTRODUCTION

Effective, less persistent alternative rodenticides to the second-generation anticoagulant brodifacoum are being sought for broad scale field control of introduced ship rats (*Rattus rattus*) and Norway rats (*R. norvegicus*) on mainland New Zealand. Diphacinone, a first-generation indandione anticoagulant, is being evaluated in this context as it is less persistent in rat liver than brodifacoum (Fisher *et al.* 2003), and has lower acute toxicity than brodifacoum to mammals and birds (U.S. EPA 1998). Alongside field assessments of the efficacy of diphacinone baits, the potential for secondary poisoning of non-target wildlife and environmental contamination resulting from the field application of baits also requires evaluation. Feral pigs (*Sus scrofa*) in New Zealand have a localized introduced pest status, but nationally they represent a resource for recreational hunters who harvest wild pork for food (McIlroy 2001). Feral pigs may be exposed to vertebrate pesticides if they access toxic baits laid for rodent control (primary exposure), or scavenge the carcasses of poisoned animals (secondary exposure). Secondary exposure of feral pigs to brodifacoum as the result of bait station applications has been reported (Morriss *et al.* 2005), highlighting the need for a proactive evaluation of the likelihood of human exposure to diphacinone residues through feral pigs. Bullard *et al.* (1976) reported that in cattle injected with 1 mg/kg diphacinone, residues were detectable in liver and kidney up to 90 days afterwards, which suggests that diphacinone could have a persistence in mammalian liver

approaching that of the second-generation anticoagulants. While the maximum residue level (MRL) for brodifacoum in meat for human consumption has been set at 0.001 ppm (the current analytical limit of detection) in New Zealand (Clear 2003), no MRL has been set for diphacinone. The New Zealand Food Safety Authority advises withholding periods for taking game from areas where vertebrate pesticides as 3 years for brodifacoum and other second-generation anticoagulants, and 2 months for pindone, warfarin, and other first-generation anticoagulants. However, no formal assessments of the persistence of sublethal exposures of diphacinone in game mammal species have been made.

The acute oral toxicity of diphacinone in pigs has previously been estimated as $\text{LD}_{50} > 150 \text{ mg/kg}$ (Hazelton Laboratories Inc. 1957). However, this estimate is not statistically strong, being based on two pigs that survived diphacinone doses of 27 and 150 mg/kg respectively, and is high in comparison with toxicity estimates available for diphacinone in other mammals. Mount and Feldman (1983) estimated an LD_{50} for diphacinone of 3-7.5 mg/kg in dogs, and Jackson and Ashton (1992) reported 1.93-43.3 mg/kg in a laboratory strain of Norway rat. Whether pigs have a particularly low single-dose susceptibility to diphacinone was worthy of further investigation. The main toxic action of anticoagulants in mammals and birds is through the inhibition of the Vitamin-K-dependent synthesis of a range of blood-clotting factors in the liver, with resultant depletion of clotting factor concentrations in blood (e.g., Thijssen 1995). This leads to increasingly

prolonged blood coagulation times, with the cause of death being massive and usually internal hemorrhage. The prothrombin time (PT) test is used to monitor the extrinsic coagulation pathway (clotting factors II, VII and X), while the activated partial thromboplastin time (APTT) test can detect abnormalities in the intrinsic coagulation pathway (clotting factors II, V, VII, IX, X, XI and XII). Together, these tests can indicate the degree to which coagulation time has been affected by a dose of anticoagulant, with extremely prolonged coagulation times indicative of a toxic effect.

The generally increased oral toxicity of first-generation anticoagulants when ingested by mammals in multiple, consecutive doses (Thijssen 1995) also needed consideration. A pen trial was planned to evaluate the toxic effects on pigs of single and multiple diphacinone exposures, simulating those that might occur if feral pigs accessed the contents of loaded bait stations in the field. Establishment of a “high” sublethal diphacinone exposure in pigs would then enable a second trial simulating a worst-case scenario for initial concentrations of residual diphacinone in live pig tissues, and measurement of their decline over time. Evaluation of the toxicokinetics of diphacinone in different tissues, including muscle and fat as those most likely to be eaten by humans, was considered a critical data requirement for risk assessments, specifically in defining a withholding period for harvesting feral pigs in areas where diphacinone bait is applied.

METHODS

Pig Housing

Domestic ‘weaner’ pigs (approximately 8 weeks old) were group-housed (maximum $n = 12$) in a 10×12 -m pen within a large shed, with wood shavings over a concrete floor and a haystack shelter. Water was freely available through an automatic drinker, and diet was commercial weaner pellets until 13 weeks old and then switched to commercial grower-and-finisher pellets (Weston Animal Nutrition, Rangiora). These feeds contained added Vitamin K₃ at 2.0-2.5 g per tonne but no added Vitamin K₁. Pigs were weighed at intervals of 7-10 days throughout the trial and fed twice daily to approximate a daily food intake of 5% bodyweight. Twelve individual feeding bays formed one wall of the pen. These were left open during 2 weeks’ acclimatization, during which pigs were trained to enter a feeding bay and have a gate closed behind them while consuming their feed. During the morning feeds of the last 10 days of acclimatization period, each pig was offered a c. 30-g ball of “sugar dough” (flour and sugar in c. 3:2 ratio, made up with water to plasticine-like consistency) prior to receiving their pellets in a feeding dish. The palatable dough was later used to deliver individual doses of diphacinone, facilitating consistent timing of total dose ingestion across treatment groups. This approach was tried in preference to offering the treatment as an unknown food type with the possible risk of rejection or partial ingestion, or attempting oral gavage with a likely handling stress to the pigs and also the risk of emesis. Pigs were individually identified by numbered plastic ear tags, and during the trial period were stock-marked with

easily visible numbers on their backs.

Range-Finding Sublethal Diphacinone Exposures Dosing

Doses were chosen to simulate relatively high field exposures of feral pigs to diphacinone baits laid for rodent control. Bait stations used in New Zealand can hold 2 kg, with 50 ppm being the usual loading of diphacinone in bait. Table 1 shows the doses given to 4 treatment groups (each $n = 3$) to which pigs were randomly allocated. The pigs were weighed in order to prepare individual diphacinone doses, according to treatment group and bodyweight. Appropriate quantities of diphacinone powder (1.98%, Animal Control Products, Wanganui) were uniformly mixed through approximately 30 g of sugar dough, which was then formed into a ball and bagged with a label indicating which numbered pig it was for. These doses were offered alongside the morning feed on appropriate day(s) (Table 1), with pigs given their pellet ration after the diphacinone dose was eaten, or if it was refused for more than 1 hour.

Table 1. Diphacinone-dosing schedule for pig treatment groups and corresponding field exposure scenario, assuming bait stations containing 2 kg of 50 ppm diphacinone bait and pigs weighing c. 40 kg.

No. Pigs (sex)	Diphacinone Dose (mg/kg) or (mg/kg/day)	Exposure Scenario
3 (2F, 1M)	12.5 mg/kg (single)	Pig accesses 5 bait stations within 1 day
3 (1F, 2M)	2.5 mg/kg (single)	Pig accesses 1 bait station in 1 day
3 (1F, 2M)	2.5 mg/kg/day (3 days)	Pig accesses 1 bait station per day for 3 days
3 (2F, 1M)	0.5 mg/kg/day (5 days)	Pig accesses c. 400 g of bait per day for 5 days

Blood Sampling

Baseline blood samples were taken 1 week before dosing with diphacinone, and then at Days 2, 7, and 14 after dosing. The pigs were restrained so that they were lying on their backs, and up to 10 ml of blood were drawn from the anterior vena cava using a 10-ml syringe and 18G \times 1½-in needle. Samples were divided between two 4.5-ml collection tubes (Vacutainer® Blood Collection Tubes, 9NC, 3.8% sodium citrate, Becton Dickinson) and stored on ice. Within 2 hours of sampling, the blood samples were centrifuged at 2,500 g for 15 minutes at 4°C. Plasma samples were aliquoted into Eppendorf tubes and stored at -80°C where testing for coagulation times could not be carried out that day, or -4°C if testing was to be done within 4 hours. To avoid death by diphacinone toxicosis as an endpoint, the Days 2 and 7 blood samples were tested within 6 hours of being taken, so that observers were aware of any pigs with elevated coagulation times. Close observation of pigs at least twice daily was undertaken over the week after dosing. In the event that a pig showed signs of anticoagulant poisoning, a licenced operator was available to perform euthanasia with a captive-bolt gun. All pigs were

euthanased in this manner at the completion of the trial, 2 days after the last blood samples were taken. Samples of liver and muscle were taken for analysis of residual diphacinone concentration as an indication of persistence that would guide the sampling intervals selected for the following trial.

Coagulation Time Tests

Munster *et al.* (2002) concluded that commercially available human coagulation assays could validly be used to test porcine plasma. One plasma aliquot from each pig at each sample interval was retained at -80°C. Where thawing was required before testing, samples were placed in a 37°C water bath. From each plasma sample, two tests of prothrombin time (PT) and activated partial prothromboplastin time (APTT) were carried out using kits (respectively Simplastin® Excel S and Platelin®, BioMérieux Inc., USA) and an automated coagulometer (Amelung KC4Amicro, Sigma Diagnostics, USA). Control plasma reagents were also tested to provide internal validation standards for the pig plasma samples. The PT times were converted to International Normalized Ratio (INR) values, by calculating the ratio of the mean PT value of the two tests for each plasma sample to the mean baseline PT (using test results from all pigs) then raised to the power of the International Sensitivity Index (ISI) figure, which was 1.23 for the Simplastin® Excel S kit. Using the statistical package R (R Development Core Team 2004), linear mixed models were fitted to the data to test for significant differences in PT, PT-INR, or APTT with respect to diphacinone dose group and days after dosing.

Persistence of Residual Diphacinone in Pig Tissues

A second group of 12 weaner pigs (6 male, 6 female) were acclimatized as before and administered a single dose of 12.5 mg/kg diphacinone in a dough ball. Coagulation time responses measured in the previous trial indicated that this represented a high sublethal intake. Pigs were randomly allocated to 3 groups (each $n = 4$) with equal sex ratios, which were euthanased by captive bolt gun on either Day 1, 4, or 10 after dosing. Livers were removed from the carcasses and weighed, and approximately 50 g retained alongside samples of muscle (from the rear haunch) and abdominal fat. Tissue samples were stored at -20°C and later analyzed for residual diphacinone by the Landcare Research toxicology laboratory using an HPLC method with a detection limit (MDL) of 0.02 µg/g and analysis uncertainty (95% confidence interval) of ±20%. An exponential decay model was used to derive equations and estimate half-life figures for residual concentrations of diphacinone in the different tissues. For tissue samples where the measured concentration was below the MDL, a value of 0.02 µg/g residual diphacinone was used.

RESULTS

Range-Finding Sublethal Diphacinone Exposures

From a mean arrival weight of 21.6 kg, the pigs gained an average of 16.6 kg each during the 27-day acclimatization and trial period. One pig (0.5 mg/kg/day for 5 days treatment) ate approximately 80% of the

treatment offered each day, so received a lower than intended overall dose, but overall, delivering treatment doses using an accustomed, palatable food was successful.

Two pigs were euthanased due to increasingly severe lameness. They were both in the 0.5 mg/kg/day for 5 days treatment, one (a female) showing slight lameness in the left hind leg on the second day of dosing, i.e. after receiving a single 0.5-mg/kg exposure, and the other (a male) lame in the right fore leg on the fifth (last) day of dosing, after having received the entire treatment. Lameness and reluctance to move became more pronounced in both pigs, with visible swelling of the affected limb and evidence of pain prompting a decision to euthanize within 48 hours of the first observation of lameness. Necropsy of both pigs revealed hemorrhage spreading from the knee or hock joint upwards along the outside of the main bone, forming an extensive hematoma mass across the muscle, which presented as visible swelling.

Mean baseline PT and APTT values were 14.94 and 33.35 seconds, respectively. Baseline INR values ranged from 0.89 to 1.14. Pigs in all treatments had PT and APTT values that were significantly higher on Day 2 than at baseline and at Day 7 and 14 (Figure 1), but there was no dose-related response. INR values in all treatments were elevated at Day 2, ranging from 2.56 to 9.84 (mean 5.57), but were back near baseline values at Day 7 and 14 (means 1.20 and 1.08 respectively). Elevated PT (64.55 and 311.25 seconds) and APTT (88.3 and 149.85 s) were measured in blood samples taken immediately post-mortem from the two euthanased pigs, with INR values of approximately 6 and 49 respectively. Liver diphacinone concentrations in the euthanased pigs were 0.7 and 0.12 µg/g, respectively. Mean liver diphacinone concentration in the remaining pigs from this trial was 0.44 µg/g, with no significant difference in the liver residue concentrations in the different treatments ($F_{3,6} = 4.25$, $P = 0.06$), indicating the persistence of a sublethal exposure of diphacinone in pig tissues was at least 2 weeks.

Persistence of Residual Diphacinone in Pig Tissues

Elimination of anticoagulants from liver typically undergoes a rapid initial phase, followed by a less steep terminal phase (Parmar *et al.* 1987). Accordingly, overall, initial, and terminal estimates of hepatic elimination half-life were made for diphacinone. Table 2 summarizes these and half-life estimates for muscle and fat, while Figure 2 shows the diphacinone concentrations detected over time in the three tissues.

DISCUSSION

Range-Finding Sublethal Diphacinone Exposures

Mean baseline PT and APTT values (14.95 and 33.35 s) in this study were similar to those previously reported (e.g., Hahn *et al.* 1996, McGlasson *et al.* 1998, Drescher *et al.* 2002), although lower normal APTT values have also been reported in pigs (Hahn *et al.* 1996, Munster *et al.* 2000). From baseline, the significant elevations of both PT and APTT at Day 2 indicated a general anticoagulant effect of all the diphacinone treatments.

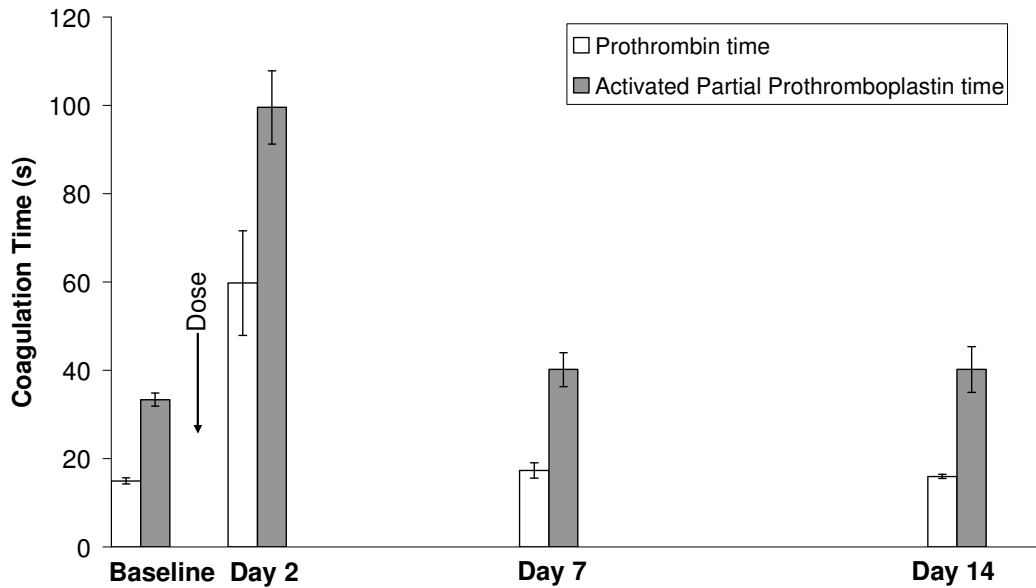


Figure 1. Mean prothrombin time and activated partial prothromboplastin time (95% confidence intervals shown as bars) of pigs before and after dosing with diphacinone. Data are pooled from pigs in all treatment groups and include baseline data from all pigs ($n = 12$) but Days 2, 7, and 14 data exclude the two pigs that were euthanased due to lameness after dosing (both from the 0.5 mg/kg/day for 5 days treatment). PT ($F_{3,27} = 62.3$, $P < 0.0001$) and APTT ($F_{3,26} = 134.6$, $P < 0.0001$) values on Day 2 were significantly different from those on Days 0, 7, and 14.

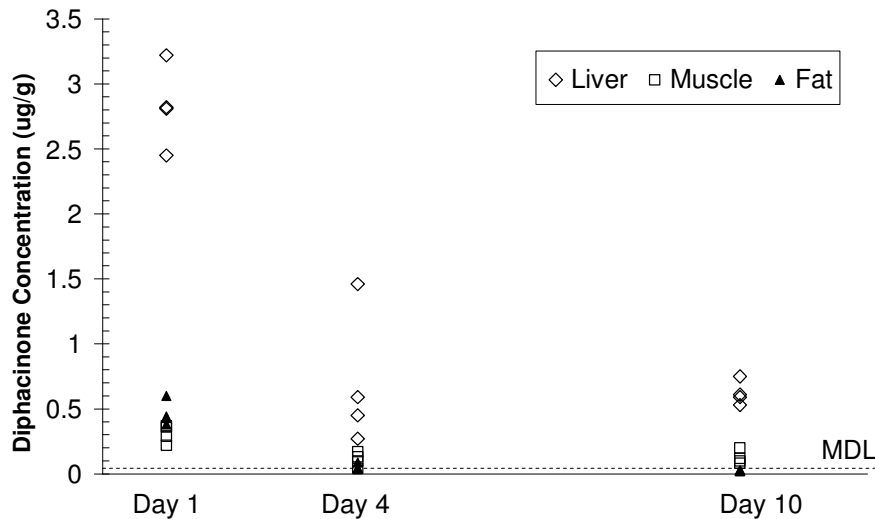


Figure 2. Concentrations of residual diphacinone in pig liver, muscle, and fat after oral exposure to 12.5 mg/kg diphacinone. Method detection limit (MDL) of 0.02 $\mu\text{g/g}$.

Table 2. Elimination half-lives with 95% confidence intervals for diphacinone in pig liver, muscle, and fat following ingestion of a single 12.5 mg/kg dose.

Tissue Type	Half-life Estimate (days)	95% Confidence Intervals
Liver	5.43 (overall)	3.55 - 11.52 days
	1.30 (initial phase over Day 1 to 4)	0.84 - 2.88 days
	14.12 (terminal phase over Day 4 to 15)	5.34 - not defined
Muscle	4.48	3.16 - 7.68 days
Fat	2.29	1.66 - 3.68 days

In human medicine, INR values of 2-3 are a “safe” therapeutic range, and values greater than 5 generally indicate a state of anticoagulation where hemorrhage is more likely to occur. Six of the 10 pigs with elevated INR values were above 5, and the remainder above 2, suggesting that at least half of the pigs were in a state of sublethal toxicosis, where no outward signs were visible but a potentially severe hemorrhage was more likely to have occurred as the result of minor injury or even normal activity. In the two pigs where severe hemorrhage occurred, the male, which had received the whole 0.5 mg/kg/day for 5 days treatment, had an “extreme” INR value of 49 just prior to euthanasia, but the female, which received only 1 day of the same treatment, had an INR value of 6, which was within the range measured in the surviving pigs. These results emphasize the unpredictability of the timing (or occurrence at all) and physiological consequence of hemorrhage during anticoagulation, but logically it is assumed that the longer elevated coagulation times are sustained, the more likely a life-threatening hemorrhage becomes.

Keith *et al.* (1990) found that oral diphacinone doses to captive wild pigs of up to 1.5 mg/pig/day for 5 days were followed by normal coagulation times at 2 and 10 days afterwards, with no signs of toxicity. Four pigs fed diphacinone at 0.333 mg/kg/day for 7 days showed some signs of poisoning, followed by recovery at 8 days after dosing, but with hemorrhage-related pathology when they were euthanased 21 days later (Fletcher 2002). In the current trial, the two pigs that developed severe hemorrhage in a leg joint had ingested substantially smaller and less prolonged doses of diphacinone than the sublethal doses given by Fletcher (2002). However, the individually-penned pigs in the latter study probably performed less weight-bearing movement than the group-housed pigs in the current study, which displayed frequent rough play, mounting and running behaviors.

Lameness appears to be a common early sign of anticoagulant toxicosis in pigs (e.g., Dobson 1973, O'Brien and Lukins 1990). At necropsy, 61.5-74.4% of 78 warfarin-poisoned pigs had fore or hind limbs affected by hemorrhage (Hone and Kleba 1984). Although this trial could not assess pig mortality as a consequence of a diphacinone exposure, the assumption is that the survival fitness of a feral pig would be compromised by lameness. Recent field data from Hawai'i show that feral pig mortality can result from primary exposure to diphacinone baits (Pitt *et al.* 2005). The results of this pen trial indicate that pigs are more susceptible to diphacinone than suggested by existing toxicity data. If this is the case, relatively high mortality could be expected if feral pigs gain access to the contents of diphacinone bait stations, or have multiple, consecutive uptakes of bait.

To date, these are the highest residual diphacinone concentrations reported in pig liver and muscle (3.22 and 0.37 µg/g respectively), occurring in one pig at 1 day after dosing with 12.5 mg/kg. The highest diphacinone concentrations in liver and muscle of a free-ranging feral pig found by Pitt *et al.* (2005) were 3.07 ppm and 0.12 ppm respectively, also co-occurring in an individual. This pig had been recently foraging on bait, with bait material found in its stomach when it was sampled, so

while the exact oral exposure was unknown, it may have ultimately been lethal. These field-based data highlight a specific ‘maximum residue’ risk consideration where a feral pig could be taken by a hunter soon after it had ingested a lethal dose, but before it had started to show obvious outward signs of poisoning.

The results reported here contrast with the findings of Bullard *et al.* (1976) in terms of expected persistence of diphacinone in mammalian liver. While no comparable half-life estimates for other anticoagulants in pigs are available, the results here are consistent with the findings of Fisher *et al.* (2003) in laboratory rats, indicating that diphacinone persistence in mammalian liver is relatively short, especially in comparison to second-generation anticoagulants. In turn, this indicates that diphacinone has a reduced potential for bioaccumulation in liver tissue. Even though muscle and fat from feral pigs are the tissues most eaten by human consumers, it is most conservative to base risk assessments on the longest persistence of residues measured—the terminal half-life estimate for diphacinone in pig liver. On this basis, it would take 104 days for the highest residue measured in liver (3.22 µg/g) to decline to just below detectable concentrations (≤0.02 µg/g). To define a withholding period for feral pigs taken for human consumption in areas where diphacinone baits have been applied, allowance should be made for the possibility of higher diphacinone residues occurring in feral pigs than were measured in pigs in this trial. By adding half again to the estimated number of days for liver residues to become undetectable, a withholding period of 156 days is suggested.

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