

# Biodeterioration of Warfarin, Sodium Monofluoroacetate (1080), 4-Aminopyridine and 3-Chloro-4-Methylbenzenamine in Terrestrial Vertebrate Pests

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## Summary

Warfarin, an anticoagulant rodenticide, is a racemic mixture of two isomers, R-warfarin and S-warfarin. Metabolites of warfarin are 6-, 7-, 8- and 4'-hydroxywarfarin. The major metabolic product of R-warfarin is 7-hydroxywarfarin and the major metabolic products of S-warfarin are 7- and 4'-hydroxywarfarin. The latter possesses one-fourth the anticoagulant activity of warfarin but the other metabolites are inactive. Scavenging mammalian predators can be poisoned by consuming animals killed by warfarin. Tissue residues of 1080, an acute rodenticide and predacide, can also poison mammalian predators although less than 3% of 1080 is converted to the toxic metabolite, fluorocitrate. The major unidentified metabolite of 1080 is nontoxic. 1080 is also metabolized into amino acids, fatty acids, and cholesterol. Comparatively little is known about the biodeterioration of the avicide 4-aminopyridine in birds and mammals, however it appears that it is not metabolized and excretion is the major mechanism for elimination. The metabolic products of another widely used avicide, 3-chloro-4-methyl-benzenamine are well known; *N*-(3-chloro-4-methyl-phenyl)acetamide, 4-acetyl-amino-2-chlorobenzoic acid and 4-amino-2-chlorobenzoic acid, although the rate and proportion vary according to the toxicological sensitivity of the individual species. Excretion rates of unassimilated chemical average 10% in all species. The potential of either avicide to cause poisoning in scavenging animals has been shown to be very low.

## I. Introduction

Pharmacodynamics, including distribution, biotransformation, and excretion, is an important parameter in determining biohazards of chemicals. This information is particularly useful for pesticides that are used in the environment to protect crops, livestock, and public health interests. Compared to insecticides, which are frequently sprayed over vast acreage, chemicals used to control terrestrial vertebrate pests are unique because they are usually applied on small areas in a manner somewhat selective for target animals. Thus, the target animal becomes the main organism for biodegrading the chemical. Upon death of the target (primary) animal, it may present a toxicity hazard to other (secondary) animals such as domestic cats and dogs or wild predators such as foxes and hawks that might prey or scavenge upon it. The degree of this secondary hazard depends upon the amount of the original chemical remaining in the target animal, its metabolic products, and their toxicity to the predatory or scavenging animal.

The four chemicals we reviewed in this paper and their current or proposed use are: warfarin (rodenticide); sodium monofluoroacetate (rodenticide, predacide); 4-aminopyridine (avicide); and 3-chloro-4-methylbenzenamine (avicide). This review presents a concise summary of the biotransformation of these chemicals and brings into perspective the secondary hazard potential of each chemical and their metabolic products.

## II. Results and Discussion

### Warfarin

Warfarin (3-(*alpha*-acetylbenzyl)-4-hydroxycoumarin), one of the most frequently and widely used rodenticides, is generally considered to have a low risk to non-target animals because it requires repeated ingestions to be toxic. It is an anticoagulant which inhibits the synthesis of prothrombin because it is an antimetabolite of Vitamin K. Warfarin contains an asymmetric carbon atom and exists as a racemic mixture of two isomers, designated as R-warfarin and S-warfarin (Fasco & Cashin 1980).

Most studies of warfarin metabolism have used acute parenteral (e.g. intraperitoneal, ip; intravenous, iv) routes, but one study (Losito & Rousseau 1972) compared  $^{14}\text{C}$ -warfarin metabolism in the rat after either iv or oral administration. Similar amounts of radioactivity were found in urine and bile with either route of administration. Although all the metabolites were not identified, there were no differences in the number of metabolites in urine or bile. Since warfarin is used primarily as a toxicant for rats, its metabolism *in vitro* in rats, without regard to route of administration, will be discussed.

Racemic  $^{14}\text{C}$ -warfarin is extensively metabolized. Urine accounts for 66% of the excretion and the feces 34% (Barker *et al.* 1979). Most radioactivity was excreted in the urine within two days with the remainder being excreted over 90 days. Radioactive urinary products were: warfarin 6.6%; 6-hydroxy-warfarin, 15.4%; 7-hydroxywarfarin, 35%; 8-hydroxywarfarin, 8.9%; 4'-hydroxywarfarin, 21%; a glucuronide of 7-hydroxywarfarin, 3.9%; and 2,3-dihydro-2-methyl-4-phenyl-5-oxo-*gamma*-pyrano(3,2-c)(1)benzopyran, 6.6%. There was no production of  $^{14}\text{CO}_2$  indicating that decarboxylation of warfarin does not occur (Losito & Rousseau 1972). Anticoagulant potency of all metabolites except the glucuronide were tested and it was found that only 4'-hydroxywarfarin possessed activity (about one-fourth that of warfarin).

There are marked age, sex, and individual differences in the rate of warfarin metabolism (Pyorala 1968). In young rats (less than six weeks old) there was no difference due to sex in the rate of metabolism, but in older rats the average plasma half-life was 18 h (range 5-70 h) in males and 28 h (range 10-90 h) in females. This difference in half-life was also reflected in the LD50 (lethal dose that kills 50% of a test population) which was three times greater in males (82 mg/kg) than in females (27 mg/kg).

Bile excretion and enterohepatic recycling are important physiological components in the metabolism of  $^{14}\text{C}$ -warfarin (Powell *et al.* 1977). It was found that warfarin and its metabolites (6-, 7-, 8-, and 4'-hydroxywarfarin) were in the form of polar labile conjugates that could be hydrolyzed by gut flora and *beta*-glucuronidase. Warfarin (24%) and 7-hydroxywarfarin (55%) comprised the two major components in bile extracts and the other three metabolites ranged from 4 to 8%. Polar glucuronide and/or sulfate conjugates of R- and S-warfarin and their metabolites have also been found in the urine (Pohl *et al.* 1976).

There is a pronounced difference in rates of metabolism between R- and S-warfarin. Breckenridge & Orme, 1972, found the plasma half-life of S-warfarin was  $15.4 \pm 2.8$  h and for R-warfarin,  $8.6 \pm 1.6$  h. Of the two isomers, S-warfarin was found to be about 6 times more potent as an anticoagulant. This potency may, in part, be due to its longer half-life. Studies by Yacobi & Levy, 1974, showed the biological half-life of S-warfarin to be 1.87 times longer than R-warfarin and there was a high statistical relationship in individual animals to the biological half-life and anticoagulant potency of each isomer; R-warfarin:  $r = 0.996$ ,  $p = 0.001$  and S-warfarin:  $r = 0.977$ ,  $p = 0.001$ . Fasco & Cashin 1980, found that a single 1 mg/kg oral dose of S-warfarin produced an anticoagulant response that equalled a single oral dose of R-warfarin at 10 mg/kg.

Stereochemical biotransformation of  $^{14}\text{C}$  R- and S-warfarin has been studied by Pohl *et al.* 1976. The major portion of both isomers was excreted in the urine and only a minor portion appeared in the feces. The major biotransformation products for either isomer in the urine were the aromatic hydroxylated metabolites (6-hydroxy-, 7-hydroxy-, 8-hydroxy-, and 4'-hydroxy R- and S-warfarins). The minor metabolites for each isomer were benzylic-hydroxy: R, S alcohol, S,R alcohol, R,R alcohol, S,S alcohol, and cyclic dehydrated warfarin alcohol. More 7-hydroxywarfarin was formed from R-warfarin than S-warfarin whereas 4'-hydroxywarfarin was formed in greater amounts from S-warfarin than R-warfarin. 7-Hydroxywarfarin was the major metabolite from either R- or S-warfarin in the urine and feces. Lewis *et al.* 1973, studied the

anticoagulant effects of warfarin alcohols in man and concluded that they contributed little, if any, to the anticoagulant activity of warfarin.

All the metabolic studies conducted with warfarin show that it is extensively metabolized and the major route of excretion is in the urine. None of its metabolites have equivalent anticoagulant activity and there does not appear to be much bioaccumulation. Although it appears that warfarin would not pose a secondary hazard, this is not always the case. Evans & Ward 1967, reported that three of three mink and one of three dogs died after eating nutria killed by warfarin. Conversely, no mortality was observed in dogs (Prier & Derse 1962) and owls (Townsend *et al.* 1981) that consumed mice poisoned by warfarin. In general, secondary poisoning from warfarin can occur in mammals if they consume poisoned carcasses over a prolonged period. Warfarin's secondary hazard to raptors appears to be low but it has not been extensively investigated.

#### Sodium monofluoroacetate

Sodium monofluoroacetate (1080) is the sodium salt of fluoroacetate (FA) which has been used effectively in both rodent and predator control programs. It is highly toxic with an acute oral LD50 of less than 10 mg/kg for most animals (Atzert 1971), but there has been a major decline in its use in favor of chemicals that are presumed to be safer. FA is well absorbed and there is no appreciable differences in toxicity between parenteral and oral administration. Based upon total organic fluorine content, which does not distinguish metabolites of FA, the recovery of FA in rats dying within 24 h after an oral dose of 3.3 mg/kg was 71%, but survivors of this dose that were sacrificed at 24 h contained only 39% of FA (Hagan 1950). These data suggest that appreciable amounts of FA would be in carcasses of poisoned animals. Except for the liver, the concentration of FA in organs (1.6-2.2 ppm) from dead rats was about two times that in sacrificed rats (0.8-1.0 ppm). The liver from both groups of rats contained the lowest amount of FA, about 0.5 ppm. In rats dosed with 5.8 mg/kg FA and sacrificed after 5 h, the liver contained 1.5 ppm and the other organs contained 5.0-10.7 ppm. Using a gas chromatographic procedure for FA (Okuno *et al.* 1984), comparable average residue levels (2.1-2.4 ppm) were detected in the muscle, heart, kidney, and intestine of coyotes poisoned with a single oral dose of 5 mg/kg. The amount in the stomach was high, 11 ppm, but the amount in the liver was low, 1.2 ppm. However, Gal *et al.* (1961) using <sup>14</sup>C-FA did not observe unequal distribution of FA in the liver of rats.

The metabolic pathway most extensively studied for FA has been its conversion of fluoroacetyl-coenzyme A and its enzymatic conversion in the Krebs Cycle to form the toxic metabolite of FA, fluorocitrate (FC), which blocks citrate metabolism by inhibition of aconitase (Peters 1952). FC has two asymmetric carbon atoms and exists as four isomers, one of which is the active form, (-)-erythrol FC (Dummel & Kun 1969).

Alternate pathways of FA metabolism have not been extensively investigated. Cell-free preparations of rat liver metabolize FA into nonsaponifiable fluoro-containing lipids that probably serve as intermediary metabolites for biosynthesis of cholesterol (Phillips & Langdon 1955). The metabolism of <sup>14</sup>C-FA after ip administration in rats was studied by Gal *et al.* (1961). About 35% of the total radioactivity was recovered in the urine four days after administration of 1.77 mg/kg. At least seven radioactive metabolites were in the urine and the major metabolite did not inhibit the activity of aconitase. The majority of the FA was excreted in one day. The amount of FC in the urine was only about 3% of the total radioactivity administered. As much as 3% of the radioactivity appeared as respiratory CO<sub>2</sub> which lends support that the C-F bond can be split. In the liver small amounts of radioactivity were found in fatty acids and cholesterol. The total amount of FC recovered in the liver was 0.16% and in the kidney it was 1.6% (Schaefer & Machleidt, 1971) using <sup>14</sup>C-FA found no evidence of FC formation from either *in vivo* or *in vitro* tests. In the *in vivo* test mice were orally dosed and no FC was found in the organs at the limit of detection, 2.5%. In the *in vitro* tests homogenates of organs from rats, rabbits, guinea pigs, and pigs were incubated and no FC was found between the detection limits of 0.06% to 0.1%. Several amino acid metabolites were detected but not chemically identified.

Defluorination of 1080 or its metabolites has been demonstrated. Egekeze & Oehme, (1979) found increased plasma and tissue fluoride concentrations in rats given acute oral doses of 1080, and rats receiving

5 ppm fluoride as sodium fluoride in drinking water for four months deposited as much fluoride in the skeletal system as rats given 5 ppm fluoride as 1080 (Smith *et al.* 1977).

Since 1080 is a non-selective toxicant and residues of it can be found in carcasses, it is not surprising that cases of 1080 secondary poisoning have been reported for coyotes, bobcats, and skunks eating 1080-killed ground squirrels (Hegdal *et al.* 1981). The amounts of FC formed from 1080 are very low and since it is not as orally toxic as 1080 (Peters *et al.* 1972), it is unlikely that FC would pose a secondary poisoning hazard. Reports on avian secondary poisoning were not found, and these types of investigations are needed to fully assess 1080 poisoning hazards in these species.

#### 4-Aminopyridine

4-Aminopyridine (4AP) is a substituted pyridine that has a high degree of acute oral toxicity to all terrestrial vertebrates with LD<sub>50</sub>'s ranging from less than 1 mg/kg to near 20 mg/kg (Schafer *et al.* 1973). Although it is used as a minor component in a number of industrial uses, the major route of exposure of terrestrial vertebrates to 4AP is through experimental use as a human drug and as an avicide.

Considerable attention has been paid to the mechanism of action of 4AP in antagonizing neuromuscular blockage caused by a variety of chemicals and clinical diseases (Foldes, 1981), but little is known about its metabolism or rate of excretion. In humans administered 20 mg 4AP iv, 65% of the administered dose was recovered in the urine within 6 h and from 80% to 91% after 24 h, indicating that much of the 4AP was being excreted unchanged. No metabolites were isolated in the serum, saliva, or urine during these studies and the authors concluded that in humans, biotransformation was unlikely (Sohn & Uges 1981, Uges *et al.* 1982).

Rupp *et al.* (1983) published the results of a similar study on dogs administered 1 mg/kg 4AP iv where serum, urine, and bile samples were collected for a period of 10 h and analyzed. Serum data for dogs, as with humans, indicate a rapid elimination of 4AP with half-lives of 1.1 min, 25.4 min and 125 min for a three-compartment model. Sixty percent of the 4AP administered appeared unchanged in the urine within 10 h and only insignificant amounts were found in the bile. Since the renal clearance of 4AP far exceeded the glomerular filtration rate, the authors determined that 4AP underwent direct tubular secretion into the urine.

Ray *et al.* (1978) reported that horses ingesting approximately 2-3 mg/kg of 0.1% 4AP-treated corn died from the treatment within 2 h. Analysis of stomach contents revealed amounts of 88.6-160 ppm 4AP, but none was found in the liver.

In a 1970 study (J.B. Sullivan, Hazelton Labs., unpublished report), fresh chicken livers were homogenized and <sup>14</sup>C-4AP was added. The homogenates were incubated at 37°C for up to 24 h with no apparent loss of radioactivity and no indication of metabolism of 4AP was found in betagrams. Another study conducted using homogenized beef livers resulted in a similar conclusion.

Frank *et al.* (1981) analyzed tissues from birds collected around sites where active bird control programs with 4AP were being conducted. They found in the short period from ingestion of bait treated with 0.030% 4AP (300 ppm) to death, 4AP residues appeared throughout the entire body. Analysis of these baits showed that they actually contained only 0.018% 4AP (180 ppm). Concentrations in the crop and gut contents averaged 15-22 ppm while residues in the remaining tissues (liver, heart, muscle, kidney, brain and lungs) average 0.8-7.6 ppm. There was little indication of species differences in the distribution or magnitude of residues in individual tissues, and whole body residues averaged 1.4-4.4 ppm 4AP. It appears that residues in the body at death are consistent with the acute oral LD<sub>50</sub> levels of 4AP and the hypothesis that little excretion and/or metabolism of 4AP takes place in the time interval between ingestion and death.

Studies with humans, dogs, chicken and beef livers and wild birds uniformly indicate that little, if any, biodeterioration of 4AP occurs in the tissues of vertebrates. Excretion in the urine, saliva and perhaps fecal material appear to be the most prevalent routes of 4AP elimination in terrestrial vertebrates.

Laboratory studies with a variety of predatory and scavenger animals have repeatedly shown a minimal potential for secondary poisoning with 4AP (Schafer, 1984), and in field use, only magpies and crows have been impacted. There is some indication that when target species are allowed to ingest 4AP-treated baits with little or no diluent present, secondary poisoning is possible in species that consume unassimilated 4AP from the gut (Holler & Schafer 1982).

### 3-Chloro-4-methylbenzenamine

3-Chloro-4-methylbenzenamine HCl (DRC-1339, Starlicide, CPTH) is an avicide originally developed to control starling damage at animal feedlots. It is unique among the more commonly used avicides because it not only possesses a high degree of selectivity between birds and mammals, but has a similar selectivity between many pest and beneficial birds (DeCino *et al.* 1966). CPTH is one of a family of biologically and chemically similar compounds that also includes 3-chloro-4-methyl-benzenamine (DRC-1347, CPT) and *N*-(3-chloro-4-methyl-phenyl)acetamide (DRC-2698, CAT). CPT and related compounds are nephrotoxic to sensitive bird species (Apostolou 1969; Giri *et al.* 1978, 1979) with acute oral toxicity levels generally less than 10 mg/kg. With non-sensitive species (some birds and most mammals), the primary cause of death (LD50's 100 mg/kg) is due to central nervous system depression (Apostolou 1969, DeCino *et al.* 1966).

In mammals two metabolites of this family of chemicals have been identified in excretia and body tissues, 4-acetylamino-2-chlorobenzoic acid (CPTC) and 4-amino-2-chlorobenzoic acid (CPTD), while CPT and CAT may also appear as metabolites of each other (Peoples & Apostolou 1967, Westberg 1969). An initial study of the metabolism of orally administered CPTH in rats indicated that CPTC and CAT were major metabolites in the liver (Peterson 1964). In a subsequent study, Westberg (1969) orally administered 250 mg/kg CPTH to rats and monitored liver, kidney, brain, and muscle residues for 2 h and found that CAT was the primary metabolite recovered, followed by smaller amounts of CPTC. No CPTD was detected and CAT and CPTC residues generally were less than CPTH although the variation between tissues over time were large. Rats dosed with 1000 mg/kg CAT showed a similar metabolite distribution, but small amounts of CPTD were found in the kidney.

Excretion of CPT and its metabolites also plays an important mechanism for the mammal to void itself of these chemicals. The half-life of CPTH in the blood of mice was estimated to be approximately 6.6 h (Felsenstein *et al.* 1974). When CPT was administered to rats at 500 mg/kg, 6% was excreted unchanged within 80 h, 8.4% as CPTC and lesser amounts as CAT and CPTD (Apostolou 1969). However, only 17% of the amount administered could be accounted for in excretia. Thin layer chromatography of urine from rats indicated the presence of at least 3 other metabolites, perhaps glucuronides or mercapturides. These unidentified compounds could also be *N*-hydroxylated or diazo metabolites similar to those formed by the mammalian liver exposed to 4-chloro-2-methylbenzamine (Hill *et al.* 1979). Rabbits orally administered 500 mg/kg CPTH excrete small amounts of CPTH and its three primary metabolites for over 24 h, mostly as CPTC (Peoples & Apostolou 1967).

The metabolism of these chemicals in the sensitive birds has been extensively studied with essentially the same results as for mammals. This is interesting in view of the apparent differences in mechanism of action and toxicity levels in sensitive and non-sensitive species. Chickens were given 15 mg/kg CPTH orally and their liver, kidney, brain and muscle tissue were monitored for 3 h for residues of CPTH and its major metabolites (Westberg, 1969). CPTC was the major metabolite found in the liver, but only CPTD was found in the kidney. No residues of either metabolite were found in the brain or muscle up to the level of detection (0.05-0.07 ppm). When chickens were also dosed with CAT, the only residues that were found were in the kidney and were either CPT or CPTD.

In one laboratory, starlings were orally dosed with 15 mg/kg CPTH and CAT and the amount and identity of each excreted metabolic product was determined for 4-5 h. In one study (Peoples & Apostolou 1967) approximately equal quantities of CPT, CPTC and CPTD were excreted over the time period and the totals represented almost the entire dose administered. An earlier study at the same laboratory indicated a 66-100% excretion of CPTH as CPT and CPTD (Peoples 1965) while a third study found essentially the same distribution of metabolites, however the total amount of chemical recovered represented less than 20% of that administered. No reasons for these differences were provided. At least two unidentified metabolites were found to be present (Apostolou 1969).

Starlings were also the subject of a number of other studies conducted to examine the tissue and body residues resulting from CPT/CAT metabolism. Peoples & Henry (1965) found that less than 10% of the originally administered CPTH was excreted before death by starlings and that less than 10% remained in the bodies of dead birds as CPT. Another study conducted by Giri *et al.* (1976) found that <sup>14</sup>C-CPTH

administered to starlings was distributed unevenly throughout the body and that the half-life of radioactivity was from 3 to 14 h, depending upon the tissues monitored. Brain and heart tissues had the shortest half-lives (3-6 h) while muscle, liver, kidney, and lung had the longest (8-14 h). Cunningham *et al.* (1980) found that starlings given 3.16-100 mg/kg CPTH retained less than 10% of the administered dose 30 min after treatment in the form of CPTH or its metabolites and that body residues of CPTH and CAT at the time of death were in the range of 1-2 ppm. These residues were not dose-dependent but were consistent across all levels.

The preceding data suggest that the known metabolic products of CPTH/CPT and CAT metabolism in birds and mammals show a great similarity, whether or not the species themselves show a sensitivity or lack of sensitivity toward these avicides. The distribution of the known metabolites and the amounts present varies considerably and is probably associated with the mechanism and sites of action. Two major metabolites (and probably 3) have not yet been identified, any of which could shed additional insight into the major metabolic pathways in these animals.

Secondary hazards of this family of chemicals has been assessed many times in the laboratory and field (Schafer 1984). Only one documented incidence of secondary poisoning occurred when crows scavenged the gut contents of pigeons killed with CPTH. Other instances of dogs, cats, hogs, owls, fox, and hawks scavenging or preying on CAT-, CPT- or CPTH-killed birds have never resulted in a confirmed case of secondary poisoning. Dermal application of this family of chemicals for avicidal properties appears to present the only real hazard to predatory or scavenger species since lethal application rates leave external body residues of 5 to 10 mg of chemical per bird. Even with dermal applications, the only species known or deemed to be at risk would be the few sensitive predatory or scavenger species such as owls and cats. Thus the relevant information on this family of chemicals indicates that: all are rapidly metabolized or excreted by all species which ingest them; known metabolites beyond CPT and CAT are essentially non-toxic to all terrestrial vertebrates; and terminal internal body residues of the more toxic chemicals at death are around 1 to 2 ppm.

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