Biological Report 20
February 1994

Contaminant Hazard Reviews
Report 27

Famphur Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review

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TABLES

FIGURE

Suggested citation:

Eisler, R. 1994. Famphur hazards to fish, wildlife, and invertebrates: a synoptic review. U. S. National Biological Survey Biological Report 20.

Famphur Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review

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Abstract

Famphur (phosphorothioic acid, O-[(dimethylamino)sulfonyl], phenyl] O, O-dimethyl ester), also known as Warbex, is a systemic organophosphorus insecticide used almost exclusively as a veterinary chemical to control parasites in livestock. Only famphur and its oxygen analog, famoxon, were of toxicological significance; other famphur metabolites were 31 to 237 times less toxic, as judged by acute oral-toxicity tests in the mouse (*Mus* sp.). Famphur is administered to livestock by intramuscular or subcutaneous injection, through the diet, as a dermal pour-on, or as an oral bolus. In mammals, famphur induced mortality at concentrations as low as 11.6 mg/kg body weight (BW) in intraperitoneal injection (mouse), 27 mg/ kg BW in a single oral exposure (mouse), greater than 33.3 mg/kg BW in an intramuscular injection (Brahman cattle, Bos *indicus*), and 400 mg/ kg BW in a dermal application (rat, *Rattus* sp.). Latent effects of famphur exposure were reported in reindeer (*Rangifer tarandus*) hinds one year posttreatment (altered blood chemistry). Famphur is rapidly metabolized by mammals, the half-time persistence of famphur and famoxon in subcutaneous fat of cattle after a single pour-on application is 0.9 days. Famphur has been used illegally by U.S. farmers to kill feral birds--including migratory waterfowl--thought to be depredating crops. Pour-on applications of famphur to cattle at recommended doses are sometimes associated with bird die-offs, especially the black-billed magpie (*Pica pica*). Magpie mortality was probably associated with the lengthy persistence (>90 days) of famphur on cattle hair and the ingestion of cattle hair by magpies. Cattle hair composed as much as 12% of gizzard contents of dead magpies, and hair in the gizzards of dead magpies averaged 4,600 mg famphur and famoxon / kg. Secondary poisoning of eagles and hawks foraging on famphur-killed vertebrates and tertiary poisoning of a great horned owl (*Bubo virginianus*) feeding on a famphur-poisoned hawk are documented. In the laboratory, sensitive species of birds died after single oral doses of 1.8-3.0 mg famphur/kg BW or when fed diets containing 35-49 mg famphur/kg ration. Depressed cholinesterase activity in the brain and in plasma occurred in nestlings at daily oral concentrations as low as 0.3 mg famphur/kg BW. No published data were available on the fate or effects of famphur in aquatic ecosystems. In the absence of aquatic toxicity data on famphur, it is recommended that famphur and famoxon concentrations do not exceed the analytical detection limits of these compounds in water (0.005 mg/ L) or in tissues of aquatic organisms (<0.01 mg/kg fresh weight). Current recommendations include the discontinuance of topical applications of famphur to cattle because of its association with primary and secondary poisoning of birds, and more research on famphur in the three areas of latent effects on treated livestock, fate and effects in aquatic ecosystems, and carcinogenicity evaluation.

Key words: Famphur, Warbex, organophosphorus insecticide, livestock, fish, wildlife, invertebrates, ecotoxicology.

Famphur (phosphorothioic acid, O,-[4-[(dimethylamino)sulfonyl], phenyl] O, O-dimethyl ester), also known as Warbex, is a systemic organophosphorus insecticide found effective against lice, grubs, flies, and gastrointestinal nematodes of ruminants. Introduced commercially in 1961, the compound is especially effective against cattle grubs (*Hypoderma* spp.) when fed in the diet, injected subcutaneously or intramuscularly, or applied as a pour-on and oral drench treatment (Gatterdam et al. 1967; Kaemmerer and Buntenkotter 1973; Black et al. 1979; Felton et al. 1981; Gallo and Lawryk 1991).

Many dead birds, including robins, hawks, and magpies were found after cattle were treated with pour-on applications of famphur (Henny et al. 1985; Smith 1987). The black-billed magpie (*Pica pica*) was especially sensitive; ranchers reported observations of magpies dying after famphur use on cattle as early as 1973 (Henny et al. 1985). Dead magpies usually had famphur in the gizzard contents and severely depressed brain cholinesterase activity--a characteristic of organophosphorus poisoning. Populations of the black-billed magpie in western states declined between 1968 and 1979, which coincides with widespread use of famphur in that region; however, factors other than famphur may have caused the decline (Henny et al. 1985).

This report was prepared in response to requests for information on famphur from environmental contaminant specialists of the U.S. Fish and Wildlife Service. It is part of a continuing series of brief reviews of chemicals in the environment with emphasis on fishery and wildlife resources.

Uses

The cholinesterase-inhibiting and intoxicating properties of organophosphorus compounds have been known since these products were first synthesized about 60 years ago (Randell and Bradley 1980). During World War II, the more toxic organophosphorus compounds--such as soman, tabun, and sarin--were stockpiled for use as potential chemical warfare agents. More than 50,000 organophosphorus compounds have been synthesized and screened for possible insecticidal and antihelminthic activity and several dozen, including famphur, are now available commercially (Randell and Bradley 1980). During the 1970's, most organochlorine insecticides were removed from common use in North America, Europe, and most developed countries, and the removal increased reliance on carbamate and organophosphorus compounds, the two major classes of cholinesterase-inhibiting pesticides (Mineau 1991). The relative lack of target specificity of these compounds and their high acute toxicity to many nontarget organisms were ignored in favor of their short-term environmental persistence and lack of accumulation in organisms. The anticholinesterase insecticides now account for the majority of globally registered insecticides (Mineau 1991).

Famphur is not now applied to forests or crops but is used almost exclusively as a veterinary chemical (Smith 1987). A single treatment controls cattle grubs and reduces cattle lice infestations (American Cyanamid Company 1984). Famphur is especially effective against maggots of the botfly and warble fly (*Hypoderma* spp.) and of other oestrid flies (Seel 1985). Eggs from this group of insects are laid on the feet and legs of cattle and other mammals and licked off by the host and hatch in the mouth or esophagus. The resultant larvae burrow through the tissues to the skin of the animal's back where they live until ready to pupate and cause warbles or swellings (Seel 1985; Tarry 1986). When applied carelessly, famphur and other systemic insecticides are highly toxic and frequently produce acute poisonings in ruminants (Ballantyne and Marrs 1992). Famphur is not now registered or regulated by the U.S. Environmental Protection Agency.

Cholinesterase-inhibiting agents such as famphur vary widely in their effectiveness of controlling target pests and depend on the route of administration, dose rate, formulation, and timing and frequency of applications (Mineau 1991). Famphur can be administered to livestock by intramuscular injection, orally in the diet, as a dermal pour-on, or as a bolus. Intramuscular injections of 35% famphur concentrate are usually given in the gluteal muscle (Loomis and Schock 1978). When fed in the diet, famphur is formulated as a 33.3% liquid feed premix (Pasarela et al. 1967; Smith 1987). The topical use of famphur as a systemic insecticide was recommended in 1970. At dosages between 15 and 35 mg/kg body weight (BW), 12.5-13.2% w/v famphur as a pour-on over part of the backline of cattle in fall controls warbles before they develop into grubs the following year (Henny et al. 1985) and controls various species of lice (Annand et al. 1976). When used as a pour-on for cattle-tick control, famphur may be transferred from treated cattle to untreated animals (Annand et al. 1976), presumably through body contact. The solvent used in preparing dermal formulations of famphur significantly affects absorption hazards. In the case of the laboratory white rat (*Rattus* sp.), corn oil proved to be the least hazardous solvent and acetone the most hazardous; benzene was intermediate (Durham 1967). Famphur can also be administered in a rumen bolus as a systemic insecticide against ticks in cattle. Boluses have been

designed to release 200 mg famphur/bolus daily over a 65-75 day post-ingestion period; actual release rates range from 207 to 308 mg daily (Hair et al. 1979).

Technical information by the American Cyanamid Company (1984) lists five precautions and warnings for the use of famphur: 1. Famphur is "Toxic to fish, birds, and other wildlife. Keep out of lakes, ponds, and streams. Do not apply to areas where run-off occurs. Do not contaminate water by cleaning of equipment or disposal of wastes." 2. After use, all containers should be drained and rinsed several times with a solution of water, detergent, and lye ("bury rinse solution deeply in an isolated location with 18 inches [7 cm] of cover"); the empty container should be punctured and crushed to prevent reuse. 3. Famphur should not be used in combination with any compound having cholinesterase-inhibiting activity either simultaneously or within a few days before or after treatment. 4. Famphur use on livestock is contraindicated for less than 3-months old calves; animals stressed from castration, dehorning, or overexcitement; and sick or convalescent animals. Brahman and Brahman crossbreeds are less tolerant of cholinesterase-inhibiting insecticides than other breeds, and Brahman bulls are especially sensitive and should not be treated with famphur. Cattle should not be slaughtered for at least 35 days after treatment with famphur. 5. For humans, famphur is considered harmful or fatal if swallowed or absorbed through the skin, especially by children. If poisoning should occur, physicians are advised that atropine is antidotal and that pralidoxime chloride may be effective as an adjunct to atropine. Pour-on formulations are flammable, and users should keep them away from heat, sparks, and open flames including hot branding irons and cautery dehorning devices (American Cyanamid Company 1984).

Chemistry and Metabolism

Some physical and chemical properties of famphur are listed in Table 1. Gas chromatography is used to measure famphur and its oxygen analog famoxon in bovine milk, blood, and edible tissues; detection limits are 0.005 mg/L milk and <0.01 mg/kg tissue (Pasarela et al. 1967; Annand et al. 1976). The main degradation routes of famphur in mammals occur through hydrolysis of the P-O phenyl, P-O methyl, and N-methyl bonds; oxidative desulfuration and N-demethylation take place to a small extent (Figure; Kaemmerer and Buntenkotter 1973; Eto 1974). In the metabolic scheme for famphur in mammals (Figure), only famphur and its oxygen analog, famoxon, were of toxicological significance, as judged by acute oral toxicity in mice (Gatterdam et al. 1967). In studies with mice, acute oral LD50 values in mg/kg BW were 27 for famphur; 18 for famoxon; 2,270 for O-desmethylfamphur; 860 for O, N-bisdesmethylfamphur; 2,290 for p-(N, N-dimethylsulfamoyl)phenol; 2,500 for p-(N-methylsulfamoyl)phenol; 6,400 for p-hydroxybenzenesulfonic acid; and greater than 5,000 for p(N,N-dimethylsulfamoyl)phenyl glucuronide.

Famphur residues of 1 to 3 mg/kg fresh weight (FW) are common in cattle tissues after normal pour-on applications of the chemical (Annand et al. 1976). The half-time persistence of famphur in subcutaneous fat of cattle after a single pour-on application was 0.9 days and was independent of dose within the range of 25 to 150 mg/kg BW or initial tissue residues between 1.8 and 12.3 mg/kg FW; fat residues were less than 0.08 mg/kg FW 5 days after treatment and less than 0.01 mg/ kg FW after 11 days. These observations suggest that famphur tissue residues are near or below detection levels within 1 week after treatment, even with gross misuse of the chemical (Annand et al. 1976). However, famphur at concentrations greater than 1,000 mg/ kg persists on cattle hair for greater than 90 days, and this persistence has serious implications for local bird populations (Henny et al. 1985).

Famphur and other organophosphorus compounds are metabolized and excreted with greater efficiency by mammals than by the target pests before these compounds can bind to and ultimately inhibit the cholinesterase enzyme (Randell and Bradley 1980). Mice, for example, degrade famphur rapidly. Less than 1 h after an intraperitoneal injection of 1 mg famphur / kg BW, only 8.34% of the original administered dose remained in the mouse: 8.11% as the parent famphur, 0.22% as famoxon, and 0.01% as desmethylfamphur (Kaemmerer and Buntenkotter 1973). Famphur's biocidal properties are associated with its ability to inhibit cholinesterase activity, blocking synapses at the neuromuscular junction. Useful and recent reviews of ecological and toxicological properties of cholinesterase inhibiting agents in the environment--including organophosphorus insecticides--are given by Gallo and Lawryk (199 1), Mineau (1991), and Ballantyne and Marrs (1992). Brain cholinesterase inhibition is often used to diagnose death of wildlife after exposure to famphur and other organophosphorus insecticides (Mineau 1991). It is emphasized that the type and number of cholinesterase compounds and cholinesterase activities vary widely between species and tissues, and activities are further modified by

metabolic factors, age, genotype, circadian rhythms, sex, reproductive status, nutritional status, ambient temperature, and disease (Mineau 1991).

Table 1. Chemical and other properties of famphur.[a]

Variable	Datum
Chemical names	Phosphorothioic acid 0-[4- [(dimethylamino) sulfonyl], phenyl] O, O-dimethyl ester; Phosphorothioic acid, O, O-dimethyl-, O-ester with p hydroxy-N, N-dimethylbenzene sulfonamide; Phosphorothioic acid, O, O-dimethyl O-p-(dimethylsulfamoyl) phenyl ester; 0 0-Dimethyl hydrogen phosphorothioate, O-ester with p-hydroxy-N, N-dimethylbenzenesulfonamide; 0-[4-1 (Dimethylamino) sulfonyl] phenyl phosphorothioic acid O, O-dimethyl ester; O, O-Dimethyl O, p-(N, N-dimethylsulfamoyl) phenyl phosphorothioate; O, p-(Dimethylsulfamoyl) phenyl O, O-dimethyl phosphorothioate; p-(Dimethylsulfamoyl)phenyl dimethyl phosphorothioate; O, O-dimethyl O-[p-(dimethylsulfamoyl)-phenyl] phosphorothioate; Dimethyl p-(dimethylsulfamoyl) phenyl phosphorothionate; O, O-dimethyl-O, p-(dimethylsulfamoyl) phenyl phosphorothionate
Alternate names	AC 38023, American Cyanamid 38023, Bo-Ana, CL 38023, Cyflee, Dovip, ENT 25644, Famaphos, Famfos, Famophos, Famphos, Fanfos, Warbex, 38023
Primary use	Systemic livestock insecticide
CAS number	52-85-7
Empirical formula	$C_{10}H_{16}NO_5PS_2$
Molelcular weight	325.36
Melting point, crystals vs. powder	52.5-53.5° C vs. 55° C
Solubility	
Chlorinated hydrocarbons	Highly soluble
Water	-100 mg/L
Polar solvents	Slightly soluble
Aliphatic hydrocarbons	Insoluble

[a] O'Brien et al. 1965; Gatterdam et al. 1967; Pasarela et al. 1967; Tucker and Crabtree 1970; Schafer 1972; Kaemmerer and Buntenkotter 1973; Eto 1974; Black et al. 1979; Ryan and McLeod 1979; Hudson et al. 1984; Hill and Camardese 1986; Smith 1987; Gallo and Lawryk 1991.

Lethal and Sublethal Effects

General

Famphur controls many species of pestiferous insects that afflict poultry and livestock. The LD50 values for target insects ranged from 2.4-4.1 mg/kg BW from a dermal route and 8.0-11.8 mg/kg BW from abdominal injection. Toxicity of famphur is often associated with differential degradation and cholinesterase sensitivity among various species of target pests. Famoxon is more effective than famphur in producing cholinesterase inhibition and death, and this confirms the generalization that the corresponding oxons are the more potent anticholinesterase agents.

No published data were available on famphur toxicity to aquatic life. Other data, however, suggest that acute famphur toxicity to fishes may be comparable to that of other phosphorothioate insecticides. Among birds, sensitive species had reduced survival after single oral doses of 1.8 to 3.0 mg famphur/kg BW or when fed diets containing 35-49 mg famphur/kg ration. Daily oral doses as low as 0.3 mg famphur/kg BW caused depressed cholinesterase activity in the brain and in plasma. Secondary poisoning of eagles and hawks foraging on famphur-killed vertebrates and tertiary poisoning of a great horned owl (*Bubo virginianus*) feeding on a famphur-poisoned hawk are documented. Famphur has also been used illegally to kill feral birds--including migratory waterfowl and other federally protected species--thought to be depredating crops. Famphur-induced mortality in mammals was documented at concentrations as low as 11.6 mg/ kg BW in intraperitoneal injection (mouse), 27 mg/kg BW in oral exposure (mouse), >33.3 mg/kg BW in intramuscular injection (Brahman cattle), and 400 mg/kg BW in dermal application (rat). In reindeer, altered blood chemistry was evident one year after famphur exposure. Famphur is metabolized rapidly by mammals; residues in animal tissues and milk--regardless of mode of administration, length of exposure, or dose--were usually not detectable within 4 days of final exposure.

Terrestrial Invertebrates

Famphur controls many species of pestiferous insects that afflict poultry and livestock, especially warble flies (*Hypoderma* spp.). Famphur is one of the most toxic compounds for the control of adults and late instars of the lesser mealworm (*Alphitobius diaperinus*), the most abundant beetle inhabiting poultry litter and manure (Vaughan and Turner 1984). *Alphitobius diaperinus* can transmit several diseases to poultry, including avian leukosis--one of the most costly diseases for the poultry industry. By tunnelling, *A. diaperinus* can destroy polyurethane and polystyrene panels adjacent to manure. Famphur also controls the lesser mealworm in nests of birds and in bat roosts (Vaughan and Turner 1984). The northern fowl mites (*Ornithonyssus sylviarum*) is the most important ectoparasite of commercial breeders and laying hens in the United States. However, attempts to control northern fowl mites with famphur were ineffective regardless of tested mode of administration (De Vaney and Ivie 1980).

Cattle lice (*Haematopinus* spp.)were controlled when the equivalent of 2.5 mg famphur/kg BW in diets was fed to cattle for at least 30 days (Ivey et al. 1976) or 40.5 mg/kg BW were applied as a topical pour-on (Randell and Bradley 1980). Famphur was used in 1971 to control cattle lice with pour-on applications equivalent to 15-35 mg/kg BW (Annand et al. 1976). Pour-on treatments of Australian yearling heifers were especially effective in controlling the long-nosed sucking louse (*Linognathus vituli*) and the short-nosed sucking louse (*Haematopinus eurysternus*); untreated heifers grew more slowly than famphur-treated heifers (Bailey et al. 1984). Larvae of the hornfly (*Haematobia irritans*) were controlled in manure of cattle fed famphur at 2.5-5.0 mg/kg BW daily (Ivey et al. 1976). Manure of treated cows contained low concentrations of famphur (as much as 0.14 mg/kg FW) 1 day after diet cessation, but residues were nondetectable thereafter (Henny et al. 1985).

In Alaska, reindeer (*Rangifer tarandus*) infested with reindeer warble flies (*Oedemagena tarandi*) produced hides of little value and low quality meat. Reindeer warble flies were not controlled by pour-on applications of famphur because the product was unable to penetrate the hair coat of reindeer; however, intramuscular injections were effective (Ivey et al. 1976). In Norway, Sweden, and Finland, famphur was the most promising control agent against reindeer warble flies and reindeer nostril flies (*Cephenomyis trompe*)--two parasites that together caused a 15 to 20% annual loss of total yield in reindeer husbandry (Nieminen et al. 1980).

Famphur was not very effective in the control of ticks. The tropical horse tick (*Anocentor nitens*) is a species of serious concern to horse breeders in Florida mainly because it transmits *Babesia caballi*, the causative agent of equine piroplasmosis. A secondary concern is that heavy tick infestations may cause injury to the ears of the

horse (Gladney et al. 1972). Data were unavailable on famphur control of ticks in horses; however, famphur was 99.9-100% effective in controlling *A. nitens* in Hereford steers and heifers when fed in the diet at 5 mg/kg BW for 14 to 21 days. Famphur at 2.5 mg/kg BW in cattle diets for 7 days was only partially effective (39-87.5%) in controlling horse ticks (Gladney et al. 1972). Famphur--despite multiple treatments--was not effective in controlling cattle ticks (*Haemaphysalis longicornis*) when used as a pour-on at recommended application rates in weaned Hereford calves (Heath et al. 1980).

Results of selected studies of famphur and insects indicate several trends: males are more sensitive than females; the oxygen analog, famoxon, is more toxic than the parent chemical; dermal LD50 values range from 2.4 to 4.1 mg/kg BW; abdominal injection LD50's range from 8.0 to 11.8 mg/kg BW; and metabolic degradation rates vary widely among species (Table 2). Famoxon is about 100 times more effective than famphur in controlling house flies (*Musca domestica*), which confirms the generalization that the corresponding oxons are the most effective anticholinesterase agents and are, in fact, the actual toxicants (O'Brien et al. 1965).

Differences in toxicity of organophosphorus compounds among species is often associated with differential degradation rates, pathways, and metabolites. Although injections of famphur were equally toxic to mice (*Mus* sp.), the American cockroach (*Periplaneta americana*), and the milkweed bug (*Oncopeltus fasciatus*), famphur was rapidly degraded by mice (91.7% degraded within 1 h after injection) and the cockroach (81.5% in 1 h); however, the milkweed bug degraded only 15.4% during a similar period (O'Brien et al. 1965). The variations in degradation rate among mice and cockroaches were relatively small, about 1.9 times. Despite the great similarity in famphur toxicity to mice and cockroaches, net famoxon production-like famphur persistence--was very low in the mouse but 10 times higher in the milkweed bug. The cholinesterase activity in the milkweed bug was 32 times more resistant to inhibition by famoxon than either mouse or cockroach cholinesterase, and this could account for the comparatively slow breakdown of famphur by the milkweed bug (O'Brien et al. 1965).

There is a correlation among cholinesterase-activity depression in rabbit blood, depression of cholinesterase activity in ectoparasites feeding on the blood of the host, and mortality of ectoparasites (Smith and Goulding 1970). In one case, rabbits (*Oryctolagus* sp.) parasitized by the yellow fever mosquito (*Aedes aegypti*)and Rocky mountain wood tick (*Dermacentor andersoni*) were treated with 5 to 50 mg of famphur/kg BW administered orally, subcutaneously, or intravenously. Regardless of dose or route of administration, tick and mosquito mortality was related to cholinesterase activity levels in rabbit plasma and erythrocytes. Some ectoparasite deaths were noted when cholinesterase levels in rabbits were depressed 32%; ectoparasite mortality increased to 90% at 33% depression and to 100% at 68% cholinesterase inhibition. In general, wood ticks and mosquitos reflected cholinesterase-activity levels of the host rabbit. Surviving female ticks that fed on dosed hosts laid no eggs during a 32-day post-removal observation period. Mosquitos that had fed on famphur-dosed hosts were more susceptible to cold than those that fed on control hosts (Smith and Goulding 1970).

Table 2. Famphur effects on selected terrestrial invertebrates.

Organism, dose, and other variables	Effect	Reference[a]
Lesser mealworm, *Alphitobius diaperinus*, topically applied		
3.44 mg/kg body weight (BW), 95% confidence interval (CI) 2.4-3.8 mg/kg BW	LD50 (24 h), adults	1
3.61 (95% CI of 3.32-4.08) mg/kg BW	LD50 (24 h), late instars	1
Milkweed bug, *Oncopeltus fasciatus*		
Abdominal injection, various doses		
Famoxon, 3.0 mg/kg BW	LD50	2

Famphur, 8.0 mg/kg BW	LD50	2
Single abdominal injection of 1 mg famphur/kg BW; whole body residues of famphur, famoxon, and N-desmethyl famphur measured 1 h after injection	Of total amount injected, 84.6% remained after 1 h: 79.4% famphur, 2.2% famoxon, and 3.1% N-desmethyl-famphur	2
American cockroach, *Periplaneta americana*		
Abdominal injection, various doses		
Famoxon, 4.6 (males) or 8.6 (females) mg/kg BW	LD50	2
Famphur, 9.0 (males) or 11.8 (females) mg/kg BW	LD50	2
Single abdominal injection of i mg famphur/kg BW; whole body residues of famphur, famoxon, and N-desmethylfamphur measured 1 h after injection	Of total amount injected, 18.5% remained after 1 h: 16.8% famphur, 0.5% famoxon, and 1.2% N-desmethyl-famphur	2

[a] 1, Vaughan and Turner 1984; 2, O'Brien et al. 1965.

Aquatic Organisms

An extensive literature search revealed no published data on famphur toxicity to aquatic animals. Unpublished studies of acute lethality were, however, conducted with bluegills (*Lepomis macrochirus*) and rainbow trout (*Oncorhynchus mykiss*). In those studies, the range in LC50 values at 96 h was 18 to 21 mg/L in bluegills and 4.9 to 5.3 mg/L in rainbow trout; the no-observable-effect concentration at 96 h ranged from 14 to 18 mg/ L in bluegills and was 2.1 mg/L in rainbow trout (U.S. Environmental Protection Agency, OPPTS/OPP / EFED / EEB, personal communication, 30 June 1993).

Although no data were available on effects of famphur in aquatic ecosystems, there is a substantial data base on other organophosphorus insecticides. For example, methyl parathion (O, O-dimethyl O-[p-nitrophenyl] phosphorothioate), another phosphorothioate organophosphorus insecticide, had LC50 (96 h) values for the bluegill (5.7 mg/L) and the rainbow trout (2.7 mg/L) that were similar to those of famphur (Khan 1977). But exposure for 96 h is not sufficient to satisfactorily evaluate the aquatic toxicity of organophosphorus insecticides. The mortality of adult northern puffers (*Sphoeroides maculatus*) continuously exposed to 20.2 mg/L of methyl parathion was less than 5% in 96 h but 100% in 40 days. Puffers refused to eat during exposure, and survivors between days 10 and 40 showed complete inhibition of serum esterase activity, zinc-depleted liver and gills, and altered blood chemistry (Eisler 1967, 1972). In another study, male guppies (*Poecilia reticulata*) held in sublethal concentrations (0.01-1.0 mg/L) of methyl parathion for 40 days or longer showed a dose-dependent decrease in spermatogenesis (Billard and de Kinkelin 1970). Pesticide-induced mortality patterns of representative organophophorus compounds are also modified by water temperature, pH, and salinity. The mummichog (*Fundulus heteroclitus*), an estuarine cyprinodontiform teleost, was most sensitive to organophosphorus compounds at elevated temperatures, reduced salinities, and low pH (Eisler 1970b). Duration of exposure to organophosphorus compounds also affects mummichog survival: fishes exposed to high (LC75, 24-h) concentrations of representative insecticides for more than 30 min died by day 21 postexposure; some insecticides were as much as 8.3 times more toxic after exposure for 240 h than 96 h, as judged by LC50 values (Eisler 1970b). In general, crustaceans were more sensitive than teleosts--sometimes by several orders of magnitude--to organophosphorus insecticides in 96-h tests; assayed grass shrimp (*Palaemonetes vulgaris*) and

fishes were most sensitive to organophosphorus insecticides at high salinities in the 1.2-3.6% test range and high temperatures in the 10-30° C test range (Eisler 1969; 1970c, 1972). Marine clams and gastropods were comparatively resistant to organophosphorus insecticides; none died in 96-h exposure to 25 mg/L of five organophosphorus insecticides, including methyl parathion. But during a postexposure of 133 days, some bivalves and gastropods died (Eisler 1970a), and these deaths are similar to the delayed mortality of some species of mammals and invertebrates after exposure to certain organophosphorus insecticides (Negherbon 1959).

The expected continued use of famphur in the environment and its vehicular transport along roads that border navigable waters suggest a need for aquatic toxicity data. Famphur data--like those on other organophosphorus insecticides-should reflect the influence of dose, exposure duration, formulation, and other biological and abiotic variables on growth, survival, and metabolism of representative species of aquatic organisms.

Birds

The avian acute oral LD50 of famphur is usually between 1 and 9.5 mg/kg BW (Schafer 1972; Hill and Mendenhall 1980). Laboratory studies with sensitive species of birds revealed reduced survival after a 5-day consumption of diets containing 35 to 49 mg famphur/kg ration (Hill et al. 1975; Table 3). Depressed cholinesterase activity in the brain and in plasma of European starling (*Sturnus vulgaris*) nestlings occurred after 15 daily oral exposures of concentrations as low as 0.3 mg famphur/kg BW (Powell and Gray 1980; Table 3). Signs suggesting famphur poisoning in mallards (Anas *platyrhynchos*) included regurgitation, goose-stepping, ataxia, wing drop, tremors, and tonic seizures (Tucker and Crabtree 1970; Hudson et al. 1984).

Famphur is considered a Class-II-toxic compound to the Japanese quail (*Coturnix japonica*) according to the classification of Hill and Camardese (1986). Class-II compounds (very toxic) kill 50% of the test organisms on diets containing 40 to 200 mg chemical/kg ration for 5 days. By comparison, the 50% kill in other classes (in mg/kg diet) is less than 40 in Class I (highly toxic), greater than 200-1,000 in Class III (moderately toxic), greater than 1,000-less than 5,000 in Class IV (slightly toxic), and greater than 5,000 in Class V (practically nontoxic; Hill and Camardese 1986). Smith (1987) rates famphur as a Class-I-toxic compound, as judged by results of dietary tests with mallards.

Birds killed by organophosphorus compounds in the wild consistently show 80 to 95% depression of brain-cholinesterase activity (Hill 1992). Depression of brain-cholinesterase activity by greater than 20% in birds has been used as a conservative criterion to indicate significant exposure to organophosphorus chemicals. Depression of brain-cholinesterase activity by greater than 50% and confirmation of suspected organophosphorus chemical residues in tissues or ingesta are criteria for cause-effect diagnosis of death in birds exposed to cholinesterase-inhibiting chemicals (Henny et al. 1985; Hill 1992). Death occurs in many avian species when brain-cholinesterase inhibition is 60 to 90%; however, no common barn-owls (*Tyto alba*) died or showed signs of intoxication after consuming famphur-poisoned Japanese quail, although 70% of the owls had brain-cholinesterase inhibition within these lethal bounds (Hill and Mendenhall 1980). Common barn-owls fed famphur-poisoned quail, the digestive tracts of which had been removed, showed significant but lesser brain-cholinesterase-activity inhibition than barn-owls fed intact poisoned quail, indicating that famphur or cholinesterase-inhibiting metabolites were most heavily concentrated in digestive tracts (Table 3).

The black-billed magpie seems unusually sensitive to famphur. Dead famphur-poisoned magpies contained as much as 290 mg famphur/kg liver FW, 4,770 mg/kg gizzard FW, and less than 0.2 mg/kg muscle or fat (Hill and Mendenhall 1980). There is a growing body of literature on adverse effects on magpies from pour-on (13.2% famphur) applications along the backline of cattle to control cattle warbles at the recommended rate of 0.326 mL/kg BW, not to exceed 118 mL/animal--equivalent to 43 mg/kg BW, not to exceed 15.6 g/animal (Felton et al. 1981; Henny et al. 1985; Seel 1985; Smith 1987). Felton et al. (1981) documented three occasions when dead birds were found after pour-on-famphur treatment of cattle against warble flies: (1) 12 black-billed magpies in a nearby field 2 to 3 days after cattle were treated; (2) 6 magpies during a 14-day period (although other species of corvids were present, only magpies were affected); and (3) 8 European robins (*Erithacus rubecula*) and a single dunnock (*Prunella modularis*) near a cattle crush a few days after famphur treatment. The dead birds had no measurable brain cholinesterase activity, and famphur was detected in the gizzards of birds in all 3 incidents (Felton et al. 1981). Partially paralyzed magpies containing as many as 3,500 mg famphur/kg gizzard contents were found in the vicinity of cattle recently treated with a pour-on formulation of famphur to control an

infestation by warble-flies; another 20 to 30 dead magpies were found in the immediate area (Seel 1985). Magpies and one red-tailed hawk (*Buteo jamaicensis*) were the only dead species found where cattle had been topically treated with famphur, although several other species including killdeers (*Charadrius vociferus*) and European starlings (Henny et al. 1985) were common in these pastures. Famphur residues were detected in all dead magpies and hawks, and brain-cholinesterase-activity depression ranged from 70 to 92%. Based on residue concentrations in the gizzards, dead magpies contained 5.2-6.1 mg famphur/kg whole body; these values were above the acute oral LD50 values for several species of birds (Henny et al. 1985; Table 3). The most probable explanation for the sensitivity of magpies to famphur is associated with the contents of the poisoned magpies that consisted of as much as 12% cattle hair (Henny et al. 1985). Although most organophosphorus compounds degrade rapidly, famphur persists for greater than 90 days on hair of Hereford bulls and steers and Angus yearlings. Famphur concentration in hair of a Hereford bull averaged 38,000 mg/kg FW one week after a single pour-on treatment and a maximum of 12,000 mg/kg FW 60 days posttreatment. High concentrations of famphur in the gizzards of magpies indicated that the material was ingested and not from dermal contact or inhalation. Tissue residues in mg famphur/kg FW in famphur-poisoned magpies were as much as 550 in the upper GI tract, 4.3 in the lower GI tract, and 3 in the whole body. Cow hair from gizzards of dead magpies averaged 4,600 mg famphur and famoxon/kg FW; other animal matter in the gizzard contained 620 mg famphur and famoxon/kg FW and plant matter 340 mg famphur and famoxon/kg FW. A potentially lethal dose to magpies would be 8-19 mg of treated hair at day 7 and 26-60 mg of treated hair after 60 days. Coincidentally, magpie mortality persisted for more than 3 months; most deaths occurred 5 to 13 days after cattle were treated (Henny et al. 1985). The manure-insect-bird pathway of famphur translocation is untenable because of extremely low (<0.14 mg/ kg FW) concentrations of famphur in cow manure (Henny et al. 1985).

Table 3. Famphur effects on birds.

Route of administration, organism, dose, and other variables	Effect	Reference[a]
Dietary exposure		
Treated feed for 5 days, then untreated feed for 3 days Mallard, *Anas platyrhynchos* 35 mg/kg diet	About 50% survived; ducklings age 10 days	1
Japanese quail, *Coturnix japonica*; 69 mg/kg diet, 95% confidence interval (CI) of 49-97 mg/kg diet	50% dead; 14-day-old quail	2
Ring-necked pheasant, *Phasianus colchicus*; 49 mg/kg diet, 95% CI of 40-61 mg/kg diet	50% dead; 10-day-old chicks	1
Domestic chicken, *Gallus* sp. Fed 50 mg/kg ration for 10 days (in attempt to control northern fowl mite, *Ornithonyssus sylviarum*) Common barn-owl, *Tyto alba*, adults, 475 g body weight (BW)	Ineffective in controlling mites. Feed consumption, body weight, and egg production significantly decreased	3

Barn-owls were fed whole famphur-poisoned Japanese quail. Quail received multiple doses of famphur (a total of 1 mg over a 3-day period). One poisoned *Coturnix* was fed daily for 10 days. If no famphur was lost or metabolized by *Coturnix* prior to death, then barn-owls received a maximum of 21 mg/kg BW for the 10-day period or 2.1 mg famphur/kg	Barn-owls did not avoid famphur-poisoned *Coturnix*, fed normally, and did not lose weight. By the tenth day, plasma-cholinesterase activities in barn-owls were depressed 45-81%, and brain-cholinesterase activities were depressed 32-73%	4
As above, except digestive tract was removed from famphur-poisoned Coturnix before presentation to barn-owls	Barn owls had brain-cholinesterase activity values intermediate between controls and those fed poisoned whole *Coturnix*	4
Multiple oral doses		
Japanese quail; dosing by gavage over 3 days: 300 µg on days 1 and 2 and 400 µg on day 3; mean weight of 120 g	Some deaths; cumulative dose received at day 3 = 8.33 mg/kg BW	4
Domestic chicken; 2.5 mg/kg BW once daily for 8 days; observed for 10 days posttreatment	Egg production, body weight, and feed consumption decreased significantly; ineffective in controlling northern fowl mite	3
European starling, *Sturnus vulgaris*, free-living nestlings, age 4 days. Dosed perorally with famphur dissolved in corn oil at 0.3, 1.0, or 3.0 mg famphur/kg BW daily for 15 days, then killed at age 19 days	At 0.3 mg/kg BW, 1 nestling died after the second dose (age 6 days) and another after the fifth dose vs. no deaths in controls; at day 19, brain-cholinesterase activity was depressed 51% and plasma activity 49%. At 1.0 mg/kg BW, 1 died after the third dose; at day 19, brain-cholinesterase activity level was depressed 75% and plasma cholinesterase 25%. At 3.0 mg/kg BW, 9 of 11 tested nestlings died within 8 h of the first dose, another within 8 h of the second dose, and the last was killed by a predator after the second dose. The 2 nestlings that survived a single dose were moribund and their brain-cholinesterase activity was depressed 85%	5

Single oral dose		
Red-winged blackbird, *Agelaius phoeniceus;* 1.8 mg/kg BW, 95% CI of 1.0-3.2 mg/kg BW	LD50	6, 9
Mallard; 9.87 mg/kg BW, 95% CI of 5.88-16.6 mg/kg BW	LD50 for 3-4 months old hens	7, 8
Domestic chicken; 10 mg/kg BW in gelatin capsule to control northern fowl mite; observed for 10 days posttreatment	Ineffective in controlling mites. On day 2 posttreatment, 1 of 12 chickens had died and 9 others showed muscular incoordination, especially in the legs. By day 3 posttreatment, most of the 9 were again standing and feeding and feces had reverted from a greenish diarrheic discharge to the normal consistency. By day 10 posttreatment, body weight and egg production was significantly decreased, although egg weight was unaffected	3
European starling; 4.2 mg/kg BW, 95% CI of 1.99-9.50 mg/kg BW	LD50	6, 9

[a] 1, Hill et al. 1975; 2, ill and Camardese 1986; 3, DeVaney and Ivie 1980; 4, Hill and Mendenhall 1980; 5, Powell and Gray 1980; 6, Smith 1987; 7, Tucker and Crabtree 1970; 8, Hudson et al. 1984; 9, Schafer 1972.

Secondary poisoning of flesh-eating birds foraging on famphur-killed vertebrates is well-documented; the degree of hazard to the predator related to the amount and type of consumed tissues and famphur concentrations in the prey tissues (Heinz et al. 1979; Hill and Mendenhall 1980; Henny et al. 1985, 1987; Hill 1992). Secondary poisoning of raptors killed by famphur that was topically applied to livestock include the bald eagle (*Haliaeetus leucocephalus*)--after eating cattle that died within 100 days of famphur treatment or famphur-poisoned brown-headed cowbirds (*Molothrus ater*) and European starlings-and a red-tailed hawk after eating famphur-poisoned black-billed magpies or European starlings (Henny et al. 1987). In one case, an adult-female bald eagle that was unable to fly near Lewes, Delaware, was brought to a national wildlife refuge where it died after a few days (Franson et al. 1985). Stomach contents included one lead shot and remains of brown-headed cowbirds and European starlings. A necropsy revealed no signs of lead poisoning. Clinical signs, physical examination, and presence of a full crop suggested acute poisoning. Crop and stomach contents were analyzed for a variety of pesticides, metals, and herbicides, but only famphur was elevated at 1.9 mg/ kg FW. As judged by famphur residues in the GI tract and by brain-cholinesterase-activity inhibition of 85%, the authors concluded that famphur was the probable cause of death (Franson et al. 1985). There is also a case of tertiary poisoning in which a great horned owl (*Bubo virginianus*) died after consuming a dead famphur-poisoned red-tailed hawk. In all of these cases brain-cholinesterase activity of poisoned birds was depressed greater than 50% and undigested remains contained famphur (Henny et al. 1987).

Famphur has also been used to intentionally kill birds, including migratory waterfowl and other protected species, and should be added to the list of other toxic organophosphorus insecticides such as monocrotophos, dicrotophos, and parathion that have been used for this purpose (White et al. 1989). In 1988, for example, famphur was used illegally by farmers in Georgia and West Virginia to kill birds thought to be depredating crops. Corn and grain at the mortality sites contained between 4,240 and 8,500 mg famphur/kg. Dead birds at these locations included Canada geese (*Branta canadensis*), mallards, American black ducks (*Anas rubripes*), American crows (*Corvus brachyrhynchos),* common grackles (*Quiscalus quiscula*), red-winged blackbirds (*Agelaius phoeniceus*), sandhill cranes (*Grus canadensis*), and a single red-tailed hawk. Most of the poisoned waterfowl, cranes, raptors, corvids, and songbirds from the 5 sites had severely depressed brain-cholinesterase activity (i.e., >50%), poisoned bait in the gizzards, and famphur concentrations in the gastrointestinal tracts ranging from 5 mg/kg FW in the red-tailed hawk to 1,480 mg/ kg FW in Canada geese. It was concluded that all birds died from direct ingestion of the poisoned bait, except the red-tailed hawk that had eaten one or more famphur-poisoned crows (White et al. 1989).

Mammals

Famphur is a group-D compound that is not classifiable as a human carcinogen (Sine 1991). However, a study of leukemia risk among males in Iowa and Minnesota indicated a slight but significant elevation in risk--especially chronic lymphocyte leukemias--for farmers but not for nonfarmers. Moreover, a significantly elevated leukemia risk was seen from exposure to specific animal insecticides including famphur (Brown et al. 1990). It is clear that more research is needed on the potential carcinogenicity of famphur.

Signs of famphur toxicosis in cattle include ataxia, muscular fasciculations, general weakness, lacrimation, salivation, and diarrhea (Randell and Bradley 1980). In comparison with European breeds of cattle (*Bos taurus*), the Brahman (*Bos indicus*) and European X Brahman hybrids are more sensitive to famphur, and Brahman bulls are more sensitive than cows (Johnson et al. 1972; Randell and Bradley 1980; Table 4). At a comparatively low dose of 16.6 mg famphur/kg BW, both *B. taurus* and *B. indicus* are tolerant of intramuscular injectable famphur; however, *B. indicus* is more sensitive and bulls sometimes died when treatment levels exceeded 33.3 mg/kg BW (Randell and Bradley 1980; Table 4). In addition to cattle, famphur-induced mortality in other species of mammals was documented (Table 4). Single exposures of famphur in mg/ kg BW killed rabbits (*Oryctolagus* sp.) at 2,730 in dermal exposure; mice (*Mus* sp.) at 27 in oral dose or 11.6 by intraperitoneal injection; domestic sheep (*Ovis aries*) at 400 in oral dose; and laboratory white rats (*Rattus* sp.) at 400 dermal exposure or greater than 28 in oral dose (Table 4). Mice receiving fatal or near-fatal intraperitoneal injections of famphur or famoxon began to convulse 10-20 min postinjection; death came within 45 min postinjection, usually from respiratory failure. Mice remaining alive at 60 min postinjection usually recovered (O'Brien et al. 1965).

Table 4. Famphur effects on mammals.

Organism, route of administration, dose, and other variables	Effect	Reference[a]
Cattle, *Bos* spp.		
Bolus		
Given to 180-kg calves 12 days before infestation by 30-60 day-old larvae of ticks. Sustained release equivalent to 3, 5, or 6.8-10.1 mg famphur/kg body weight (BW) daily	Ineffective at 3 mg/kg BW against fever ticks (*Boophilus annulatus*, *B. microlopus*) and the American dog tick (*Dermacentor variabilis*). At 5 mg/kg BW, famphur was effective (87-97%) against fever ticks but ineffective against the dog tick. At the highest daily release rate, famphur was 100% effective against fever ticks between	1

	days 12 and 41 but remained ineffective against the dog tick	
7 mg/kg BW daily (range 4.5-11.5 mg/kg BW daily)	Bolus was 99-100% effective against Gulf Coast tick (*Amblyomma maculatum*) and 60-86% effective against the lone star tick (*A. americanum*). Heifers showed no signs of organophosphorus insecticide poisoning but had slight reduction in erythrocyte-cholinesterase activity	2
Diet		
Lactating cows fed diets equivalent to 3.3 mg famphur/kg BW for 90 days	Concentrations in milk on day of withdrawal were 0.025 mg famphur/L and 0.023 mg famoxon / L. During the next four milkings (i.e., through day 8 posttreatment), famphur and famoxon residues in milk were always <0.005 mg/L	3
Calves fed rations equivalent to 3.3 or 9.9 mg famphur/kg BW for 90 days	Within 2 days of cessation of the low-dose-contaminated diet all calf tissues were free of famphur and famoxon; this value was 4 days for the 9.9 mg/kg BW group. Concentrations of famphur (famoxon) in mg/kg FW in the high-dose group at the end of the 90-day feeding study were 0.31 (0.03) in muscle, 1.6 (0.23) in fat, 5.6 (0.5) in liver, and 0.49 (0.19) in kidney	3
Adult rations contained equivalent of 5 mg famphur/kg BW daily	99.5-100% effective in control of Gulf Coast tick and lone star tick; ineffective against the American dog tick	1
Adults given equivalent of 5 mg famphur/kg BW daily	Effective against tropical horse tick (*Anocentor nitens)* but not completely effective against 3 other species of ticks	2
Adults given equivalent of 5 mg/kg BW daily for 10 days,	>90% control of cattle grubs (*Hypoderma* spp.). Manure from treated cattle	4

administered as a 33%-feed premix	controlled larvae of horn fly (*Haematobia irritans*) but was ineffective against larvae of the house fly (*Musca domestica*)	
Intramuscular injection		
15 mg/kg BW; Hereford steers	97% grub reduction in calves, 93% in cows, and calves, Angus cows; to 94% in steers control cattle grubs (*Hypoderma lineatum, H. bovis*)	5
16.6, 33.3, or 49.9 mg/kg BW, single injection; Brahman bulls, steers, and heifers 6-8 months old, 169-200 kg BW. Observed for 28 days posttreatment	All doses inhibited erythrocyte-cholinesterase levels by 45-95%. All groups tolerated 16.6 mg/kg BW. Severe toxicosis in the two high-dose groups (9 of 20) in bulls but not in heifers and steers; 7 of the 9 bulls died or had to be euthanized; necropsy showed severe pulmonary edema	6
18 mg/kg BW, single injection	Residues <0.7 mg/L in blood 2 h postinjection	7
36 mg/kg BW, single injection	Residues in blood >0.7 mg/L 2 h postinjection, but <0.7 mg/ L after 4 h	7
54 mg/kg BW, single injection	Residues in blood >0.7 mg/L 1-2 h postinjection, but <0.7 mg/L after 4 h	7
60.7 mg/kg BW, single injection of radiolabeled famphur	Blood plasma levels in mg/kg fresh weight (FW) were 0.4 after 4 h and 0.18 after 72 h; for famoxon, these values were not detectable at 4 h and 0.05 at 72 h. Plasma and urine radioactivity levels reached maxima after 24 h	7, 8
83.2 mg/kg BW; Brahman bulls and Angus bulls, 7-9 months old, 174-184 kg BW	5 of 6 injected Brahman bulls showed severe signs of toxicosis and 4 died within 48 h; recovery of the 5th bull took 10 days. Only 1 of 5 Angus bulls showed clinical signs of toxicosis, but it recovered	6
Oral		
9.9 mg/kg BW; single application, residues measured 24 h posttreatment; control values always <0.05 mg / kg FW of famphur and famoxon		
Fat; famphur vs. famoxon (mg / kg FW)	0.14 vs. <0.05	3

Kidney; famphur vs. famoxon (mg / kg FW)	<0.05 vs. <0.05	3
Liver; famphur vs. famoxon (mg / kg FW)	0.08 vs. 0.05	3
Muscle; famphur vs. famoxon (mg/kg FW)	<0.05 vs. <0.05	7
18 mg/kg BW	Residues in blood >0.7 mg/L 18-24 h after ingestion	7
20, 30, or 40 mg/kg BW, each with 8 mg levamisole / kg BW; administered as a paste to cattle yearlings in California, Nebraska, and Kentucky	As much as 85% reduction in cattle grubs and nematode gastrointestinal worms at 20 mg / kg BW + levamisole; as much as 98.2% reduction in 30 or 40 mg/kg BW groups	9
36 mg/kg BW, single dose	Residues in blood >0.7 mg/L 6-72 h after intake, but <0.7 mg/L after 96 h	7
Pour-on		
15 to 35 mg/kg BW, cows	Controls cattle-biting lice (*Damalina bovis*), long-nosed cattle lice (*Linognathus vituli*), and short-nosed cattle lice (*Haematopinus eurysternus*)	10
20.25, 40.5, or 60.75 mg/kg BW; Holstein Friesian calves; blood-cholinesterase-activity levels measured up to 49 days posttreatment	At the 2 lowest doses, significant depression from day 2 through day 14; blood cholinesterase normal at day 21. At 60.75 mg/kg, blood cholinesterase decreased for entire 49-day posttreatment. No outward signs of organophosphate intoxication and normal food intake and demeanor	11
23 mg/kg BW, cows	At 24 h whole milk had 0.24 mg famphur/L of which 76% was in the butterfat fraction; after 72 h residues in milk were <0.008 mg/L	10
25 mg/kg BW, cows	After 24 h, mean residue of famphur in subcutaneous fat was 1.8 mg/kg FW, maximum was 2.46 mg/kg FW	10
40 mg/kg BW; Hereford	87% effective in controlling cattle	5

steers and calves, Angus cows	grubs in calves; 100% effective in cows and steers	
40 mg/kg BW, cattle yearlings	100% effective in controlling cattle grubs and nematode gastrointestinal worms	9
40 or 50 mg/kg BW; yearling steers; Canada, late autumn; single treatment	Although not completely satisfactory for control of *Hypoderma* spp. (52-68% reduction in grubs)--possibly because of low absorption associated with low ambient temperatures at time of treatment--and some inhibition in blood-cholinesterase activity (maximum inhibition of 31-38% reached 15 days after treatment), both groups of treated steers gained significantly more weight than a control group during the posttreatment of 181 days and were otherwise normal	12
40, 80, or 209 mg/kg BW; Brahman bulls, steers, and heifers; mean weight of 117 kg		
40 mg / kg BW	Erythrocyte cholinesterase depression after 24 h was 43% in bulls and 33-34% in steers and heifers	13
80 mg/kg BW	After 5 h, 1 of 13 bulls was anorexic and salivating	13
209 mg/kg BW	After 48 h, erythrocyte-cholinesterase depression was 56% in bulls, 55% in steers, and 51% in heifers.	13
40.5 mg/kg BW, Brahman bull calves	2 of 3 famphur-treated calves died	11
45 mg/kg BW, cows	Famphur concentrations in mg/kg FW after 24 h were <0.05 in liver and kidney, 1.25 in fat, and 1.41 in muscle. After 7 days, these values were 0.53 in fat and 0.71 in muscle. By day 14, maximum values were 0.11 mg / kg FW in fat and <0.02 in other tissues	10
50 mg/kg BW, cows	After 24 h, mean residue of famphur in subcutaneous fat was 2.08 mg/kg	10

	FW, maximum was 3.00 mg/kg FW	
150 mg/kg BW, cows	After 24 h, famphur concentrations in subcutaneous fat ranged from 6.3 to 12.3 mg/kg FW	10
Angora goat, *Capra* sp.; pour-on, 4.1-4.8 mg/kg BW; nannies 27-41 kg; single application	100% effective in 14-day control of Angora goat biting louse (*Bovicola limbatus*) and hairy goat louse (*B. crassipes*); significant protection after 45 days	14
Laboratory mouse, *Mus* sp.		
Dermal; mice infected nasally or orally with rodent botfly (*Cuterebra* sp.) were dipped 48 h post-infestation for 30 sec in 25% emulsifiable famphur solutions (0.001-10%) and examined 1 week later. Entire body was submersed except head	50% kill of larvae after immersion in 0.0072% solution (18 mg famphur / L); 90% control in 0.051% solution (127.5 mg/L)	16
Oral		
Male mice, 8-12 weeks old, orally and nasally infected with 1st-stage larvae of rodent botfly. Two days after infection, mice were given single doses of 1.46 or 3.38 mg famphur / kg BW	Low dose killed 50% of larvae; high dose killed 90%	17
As above, except that mice were given 1.5 mg famphur/kg BW at 1, 2, or 3 days after infestation	Most effective control (71% dead larvae) when administered at 3 days	17
18 mg/kg BW	Acute LD50, famoxon	7
27-30 mg/kg BW	Acute LD50, famphur	7, 15
Intraperitoneal injection		
Single injection of 1 mg famphur/kg BW; residues of famphur, famoxon, and N-desmethylfamphur measured 1 h post-injection	Only 8.3% of the injected dose was measurable 1 h post-injection: 8.1% as the parent famphur, 0.2% as famoxon, and 0.01% as N-desmethylfamphur	18
5.8 mg famoxon/kg BW	LD50	18
11.6 mg famphur/kg BW	LD50	18
Rabbit, *Oryctolagus* sp.		
50 mg/kg BW; oral, subcutaneous, or	No effect on reproduction	25

intravenous route		
2,730 mg/kg BW, dermal route	LD50	15
Domestic sheep, *Ovis aries*		
Bolus; sustained release of 7 mg famphur/kg BW daily	Completely effective against Gulf Coast tick, partial control of lone star tick,	2
Intravenous injection	ineffective against American dog tick	
Single injection of radiolabeled famphur equivalent to 22.3 mg famphur/kg BW. Sheep killed at 96 h and tissues analyzed for residual radioactivity	More than 50% of the administered dose was excreted within 6 h and 98% within 48 h. About 97% was excreted in urine and <3% in feces. Residues, in mg/kg FW, were 1.4 in blood; 0.3 to 0.6 in kidney, liver, spleen, lung, and cerebrospinal fluid; and <0.1 in bile, fat, brain, and muscle	7, 8
Single injection, 22.3 mg/kg BW	Famphur (famoxon) residues in blood plasma, in mg/kg FW, were 0.6 (5.6) at 2 h, and nondetectable (0.01) at 24 h	7
Intravenous or intramuscular injection; urine collected over 24-h period after single application of radiolabeled famphur	Urinary radioactivity was due to the unchanged O-desmethyl compound (13-24%); N, N-dimethyl sulfamoylphenyl glucuronide (32-33%); O, N-bisdesmethylfamphur 31-34%); and N-methyl sulfamoylphenyl glucuronide (8-15%)	8
Intramuscular injection		
Single injection of radiolabeled famphur, equivalent to 55.1 mg/kg BW. Sheep killed at 72 h and tissues analyzed for residual radioactivity	About 64% of the administered dose was recovered in excreta after 72 h. Residues in mg/kg FW were 15 at the muscle injection site; 5-8 in kidney, bile, and fat; 1.6-2.3 in liver, spleen, lung, and blood; and 0.7-0.9 in brain, muscle, and cerebrospinal fluid	7, 8
Single injection, 55.1 mg/kg BW	Famphur (famoxon) residues in blood plasma, in mg/kg FW, were 0.9 (0.1)	7, 8
Oral, single dose; 400 mg/kg BW	LD50	15, 19, 20
Rumen infusion; peroral administration by cannulation for 72 h of ewes given doses equivalent to 5 or 7 mg	At 5 mg/kg BW, famphur caused a significant increase in mortality and decrease in percent egg hatch of adult Gulf Coast ticks and complete control	21

famphur/kg BW daily. After infusion for 72 h sheep were challenged by various blood-sucking arthropods	of the bedbug (*Cimex lectularius*) At 7 mg/kg BW daily, Gulf Coast ticks were completely controlled, but dose was ineffective against the lone star tick and the American dog tick	
Reindeer, *Rangifer tarandus*; intramuscular injection		
15 mg/kg BW, single injection	At 24 h residues were highest (8.1-9.1 mg/kg FW) in fatty tissues; at muscle injection site, residues ranged up to 635 mg/kg vs. 0.6 mg/kg FW in normal muscle. At 7 days post-treatment, residues in mg/kg FW, were 0.03-0.19 in fat, 0.03 in injection-site muscle, and 0.03 in liver. At 5 weeks, famphur was detectable only in fat; by 7 weeks, no famphur was detectable in any tissue. Famoxon was not found in any tissue at any time	22
30 mg/kg BW, single injection	Residues at 24 h in mg/kg FW were as high as 38 in fat, 8 in muscle, 5 in liver and 2.5 in kidney	22
30 mg/kg BW, single injection	90-95% reduction in larvae of warble fly (*Oedemagena tarandi*) and nostril fly *(Cephenomyia trompe*)	23
Accidental overdose (usually double-dosed), 60 mg/kg BW	Atropine sulfate is recommended antidote	23
Laboratory white rat, *Rattus* sp.		
Dermal, single application, mg/kg BW		
400	LD50, adult males	19
533	LD50, adult females	19
Diet containing 1, 3, or 25 mg famphur/kg for as many as 90 days	At 90 days all groups had depressed plasma cholinesterase, although growth and appetite seemed normal. Whole blood cholinesterase was depressed in the 3 and 25 mg/kg group; brain cholinesterase was significantly reduced in the 25 mg/kg group	24
Diet containing 25 mg famphur/kg for 90 days,	Blood chemistry and histology normal at necropsy on day 132. Rats avoided diets	24

then famphur-free diet for 42 days	during famphur-free phase	
Oral, single dose, in mg/kg BW		
28	LD50, adult males	19
35	LD50	7, 20
36-62	LD50	15
51	LD50, adult females	19
73	LD50, weanling males	19
Subcutaneous injection; urine collected during 24 h period after single application of radiolabeled famphur	Urinary radioactivity was due to the unchanged O-desmethyl compound (>50%); N,N-dimethyl sulfamoylphenyl glucoronide (30%); O,N-bisdesmethylfamphur (12%), and N-methyl sulfamoylphenyl glucuronide (7%)	8

[a] 1, Hair et al. 1979; 2, Teel et al. 1979; 3, Pasarela et al. 1967; 4, Drummond 1968; 5, Loomis and Schock 1978; 6, Randell and Bradley 1980; 7, Kaemmerer and Buntenkotter 1973; 8, Gatterdam et al. 1967; 9, Campbell et al. 1987; 10, Annand et al. 1976; 11, Watson and Black 1981; 12, Khan and Kozub 1981; 13, Johnson et al. 1972; 14, Fuchs and Shelton 1985; 15, Smith 1987; 16, Drummond and Gingrich 1972; 17, Gingrich et al. 1972; 18, O'Brien et al. 1965; 19, Gallo and Lawryk 1991; 20, Eto 1974; 21, Teel et al. 1977; 22, Ivey et al. 1976; 23, Nordkvist 1975; 24, Black et al. 1979; 25, Smith and Goulding 1970.

Latent effects of famphur exposure in reindeer hinds (Nieminen et al. 1980) strongly indicated a need for additional studies in this subject area. Intramuscular injections of reindeer hinds and their 4-week-old calves controlled warble-fly infection in treated animals. Treated calves did not differ significantly from controls during the following year in body weight, body temperature, or blood chemistry. Treated hinds, however, had significantly lower erythrocyte sedimentation rates and serum-gamma-globulin concentrations and significantly higher hemoglobin, serum calcium, serum inorganic phosphorus, and serum magnesium than untreated hinds 1 year after treatment (Nieminen et al. 1980).

Reduced brain-cholinesterase activity in avian and mammalian wildlife is associated with adverse effects on metabolism, reproduction, sensory behavior, motor activity, food and water intake, learning, and memory (Mineau 1991). Cholinesterase activity in mammals regenerates rapidly after a cessation from treatment with famphur (Kaemmerer and Buntenkotter 1973). In humans, typical symptoms of organophosphorus-induced cholinesterase inhibition include headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps, diarrhea, chest discomfort, sweating, salivation, vomiting, and tremors (Gallo and Lawryk 1991). In severe cases, victims show muscular weakness, convulsions, coma, loss of reflexes, loss of sphincter control, and eventually death. Effects of cholinesterase-inhibiting agents in humans are usually counteracted with repeated intravenous injections of atropine sulfate (2-4 mg), intravenous injections of pralidoxime chloride (1 g), and oxygen (Gallo and Lawryk 1991). Rats had depressed plasma-cholinesterase activity when fed diets containing as little as 1 mg famphur / kg for as many as 90 days, although growth and appetite seemed normal (Black et al. 1979). Brahman bulls had maximum erythrocyte-cholinesterase inhibition 14 days after intramuscular injection of famphur; cholinesterase-activity levels recovered towards normal during the next 14 days, and recovery correlated with the formation of new erythrocytes (Randell and Bradley 1980). Except for cholinesterase-activity inhibition, there were no signs of organophosphate intoxication in Brahman heifers and steers given single dermal doses of 20 to 61 mg famphur/kg BW. Cholinesterase activity was inhibited for as many as 14 days posttreatment at the lower (20-41 mg/kg BW) doses and for at least 7 weeks at 61 mg/ kg BW (Table 4).

Famphur is metabolized rapidly in mammals. In cattle, famphur controlled target insect pests when administered as a bolus, in the diet, as an oral paste, by intramuscular injection, or by pour-on. Regardless of mode of administration, length of exposure, or dose, famphur residues in tissues and milk were usually nondetectable within 4 days of final exposure. A similar pattern was evident in other species of mammals (Table

4). Rats and sheep metabolize famphur differently. During the first 24-h postdosing period, urine of rats contained as much as 2 times more of the unchanged O-desmethyl compound than urine of sheep, about the same amount of dimethylsulfamoylphenyl glucoronide, about 0.3 times as much O, N-bisdesmethylfamphur, and about 0.5 times less methylsulfamoylphenyl glucoronide (Gatterdam et al. 1967). With the exception of the oxon, metabolites of famphur were considerably less toxic to mammals than the parent chemical. In general, famoxon was 100 times more effective than famphur in depressing erythrocyte-cholinesterase activity (Kaemmerer and Buntenkotter 1973).

Famphur in pour-on applications penetrates skin at different rates depending on the solvent. In rat skin, penetration was most rapid when the solvent was acetone and least rapid in corn oil and benzene; the percent of remaining famphur in rat skin 3 h after a single dermal application was 38% from the acetone mixture and 67% from both benzene and corn oil solvents (O'Brien and Dannelley 1965). The penetrability of famphur pour-on formulations used in lice control on Angora goats was enhanced when applied in combination with a liquid-detergent wetting agent (Fuchs and Shelton 1985). Laboratory screening tests in which small mammals are treated with chemicals and parasitized by insects are now used to predict the effectiveness of systemic insecticides. Tests with mice and rodent botfly (*Cuterebra* sp.) were useful in predicting the effectiveness of famphur against larvae of the common cattle grub (*Hypoderma lineatum*) in cattle (Gingrich et al. 1972; Table 4), and show promise for screening additional chemicals.

Recommendations

The four primary areas of concern about famphur use are (1) mortality of birds associated with topical applications to cattle; (2) latent effects on domestic livestock; (3) the absence of aquatic toxicity data; and (4) potential carcinogenicity.

Because of its high toxicity to birds and field and experimental evidence of primary and secondary poisoning of birds, famphur is considered hazardous to feral birds--especially magpies-where cattle are topically treated with this insecticide (Felton et al. 1981; Henny et al. 1985, 1987). The pour-on application for cattle is now preferred to systematic dipping or intramuscular injection; dipping is reportedly labor intensive and costly (Hair et al. 1979). Intramuscular injection is more labor intensive, causes greater tissue damage and higher famphur absorption at the injection site, and produces a greater depression in blood-cholinesterase levels and a lower rate of weight gain in cattle than pour-on application (Loomis and Schock 1978). Nevertheless, famphur-induced mortality of magpies and other birds can be significantly reduced or eliminated by changing the insecticide application from the present pour-on method to other, now available modes of administration such as by diet, bolus, and intramuscular injection (Henny et al. 1985, 1987). Furthermore, a warning should be added to famphur labels stating that livestock dying within 3 months of famphur treatment should be removed from the range or farmland; this would offer partial protection to carrion-eating raptors such as eagles and vultures (Henny et al. 1987).

Reindeer are considered safe for human consumption 6 to 7 weeks after famphur treatment by intramuscular injection (dermal applications of famphur seldom penetrate the thick hair coat of reindeer). Treated reindeer had no detectable residues in liver, kidney, and muscle after 3 weeks (Ivey et al. 1976) and none in fat and other tissues after 6 to 7 weeks (Nordkvist 1975; Ivey et al. 1976). However, treated hinds during the following year had a significantly greater altered blood-chemistry profile than untreated hinds (Nieminen et al. 1980), suggesting a need for additional research on latent effects of famphur exposure. A safe dosage for cattle (*Bos* spp.) is 7 to 25 mg/kg BW by intramuscular injection or 40-55 mg/ kg BW by pour-on (Loomis and Schock 1978). The maximum concentration of famphur and famoxon allowed in cattle meat, fat, and meat by-products in the United States is 0.1 mg/ kg (Kaemmerer and Buntenkotter 1973; Ryan and McLeod 1979). In Australia, the maximum value is 0.05 mg/kg FW (Annand et al. 1976). The recommended minimum time between famphur treatment and slaughter of Australian cattle is 14 days. The half-time persistence of famphur in cattle tissues is 0.9 days, implying that even with gross misuse of the chemical, residues fall to low levels within a week (Annand et al. 1976). At present, no published studies were available on latent effects of famphur to cattle. Evidence of latent effects of famphur in reindeer (Nieminen et al. 1980) strongly suggest initiation of research into this subject area with cattle and other treated livestock.

No published data were available on effects and fate of famphur in aquatic ecosystems. This seems to be a high-priority research need in view of the increasing and illegal use of famphur to kill migratory waterfowl (White et al. 1989). In the absence of these data, it is recommended that concentrations of famphur and famoxon in

water and in tissues of aquatic organisms not exceed current analytical detection limits of 0.005 mg/L in water or 0.01 mg/kg FW tissue.

The carcinogenicity of famphur has not been satisfactorily resolved. Recent studies indicate a significantly elevated risk for leukemias among farmers handling famphur (Brown et al. 1990), but this needs verification.

Acknowledgments

I thank L. Garrett and W. Manning for literature search and retrieval services; M. G. Holmes for secretarial assistance; and A. J. DeLonay, C. J. Henny, P. F. P. Henry, E. F. Hill, and three anonymous referees for technical review of the manuscript.

Cited Literature

American Cyanamid Company. 1984. Warbex (famphur) pour-on for cattle 13.2%. American Cyanamid Company, ANH-19002, 4/87, TCEM. 2 pp.

Annand, A. M., J. H. P. Dingle, A. B. Heath, and W. A. Palmer. 1976. Residues of famphur in bovine tissues and milk following its application as a pour-on insecticide. Australian Journal of Experimental Agriculture and Animal Husbandry 16:82-87.

Bailey, P. J., W. A. D. Carroll, and B. Knee. 1984. Effects of lice infestation on the growth of beef heifers in Victoria. Australian Journal of Experimental Agriculture and Animal Husbandry 24:140-143.

Ballantyne, B., and T. C. Marrs, editors. 1992. Clinical and experimental toxicology of organophosphates and carbamates. Butterworth-Heinemann, Oxford, England. 641 pp.

Billard, R., and P. de Kinkelin. 1970. Sterilisation des testicules de guppies par des doses non letales de parathion. Annales d'Hydrobiologie 1:91-99.

Black, W. D., V. E. Valli, M. J. Claxton, and M. L. Marceau-Day. 1979. The effects of the subchronic feeding of the organophosphate famphur to rats. Toxicology and Applied Pharmacology 50:167-170.

Brown, L. M., A. Blair, R. Gibson, G. D. Everett, K. P. Cantor, L. M. Schuman, L. F. Burmeister, S. F. Van Lier, and F. Dick. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Research 50:6585-6591.

Campbell, J. B., F. W. Knapp, E. C. Loomis, D. J. Boxler, F. Herald, and L. L. Dunning. 1987. Efficacy of levamisole/famphur paste for control of cattle grubs (Diptera: Oestridae) and gastrointestinal worms (Nematoda: Trichostrongylidae). Journal of Economic Entomology 80:1028-1030.

De Vaney, J. A., and G. W. Ivie. 1980. Systemic activity of coumaphos, famphur, crufomate, ronnel, and phosmet given orally to hens for control of the northern fowl mite, *Ornithonyssus sylviarum* (Canestrini and Fanzago). Poultry Science 59:1208-1210.

Drummond, R. O. 1968. Further evaluation of animal systemic insecticides, 1967. Journal of Economic Entomology 61:1261-1264.

Drummond, R. O., and R. E. Gingrich. 1972. Detection of systemic activity of insecticides applied dermally to white mice infested with larvae of Cuterebra sp. Journal of Economic Entomology 65:1211-1212.

Durham, W. F. 1967. The interaction of pesticides with other factors. Residue Reviews 18:21-103.

Eisler, R. 1967. Tissue changes in puffers exposed to methoxychlor and methyl parathion. U.S. Bureau of Sport Fisheries and Wildlife Technical Paper 17. 15 pp.

Eisler, R. 1969. Acute toxicities of insecticides to marine decapod crustaceans. Crustaceana 16:302-310.

Eisler, R. 1970a. Latent effects of insecticide intoxication to marine molluscs. Hydrobiologia 36:345-352.

Eisler, R. 1970b. Factors affecting pesticide-induced toxicity in an estuarine fish. U.S. Bureau of Sport Fisheries and Wildlife Technical Paper 45. 20 pp.

Eisler, R. 1970c. Acute toxicities of organochlorine and organophosphorus insecticides to estuarine fishes. U.S. Bureau of Sport Fisheries and Wildlife Technical Paper 46. 12 pp.

Eisler, R. 1972. Pesticide-induced stress profiles. Pages 229-233 *in* M. Ruivo, editor. Marine pollution and sea life. Fishing News (Books), London.

Eto, M. 1974. Organophosphorus pesticides: organic and biological chemistry. CRC Press, Cleveland, Ohio.

Felton, C. L., P.M. Brown, M. R. Fletcher, and P. I. Stanley. 1981. Bird poisoning following the use of warble fly treatments containing famphur. Veterinary Record 108:440.

Franson, J. C., E. J. Kolbe, and J. W. Carpenter. 1985. Famphur toxicosis in a bald eagle. Journal of Wildlife Diseases 21:3 18-320.

Fuchs, T. W., and M. Shelton. 1985. Effectiveness of new methods of biting lice control on Angora goats. The Southwestern Entomologist 10:15-19.

Gallo, M. A., and N.J. Lawryk. 1991. Organic phosphorus pesticides. Pages 917-1123 *in* W. J. Hayes, Jr., and E. R. Laws, Jr., editors. Handbook of pesticide toxicology. Volume 2. Classes of pesticides. Academic Press, New York.

Gatterdam, P. E., L. A. Wozniak, M. W. Bullock, G. L. Parks, and J. E. Boyd. 1967. Absorption, metabolism, and excretion of tritium-labeled famphur in the sheep and calf. Journal of Agricultural and Food Chemistry 15:845-853.

Gingrich, R. E., O. Drummond, and W. J. Gladney. 1972. Use of white mice experimentally infested with larvae of a rodent botfly for screening systemic insecticides. Journal of Economic Entomology 65:742-745.

Gladney, W. J., S. E. Ernst, C. C. Dawkins, R. O. Drummond, and O. H. Graham. 1972. Feeding systemic insecticides to cattle for control of the tropical horse tick. Journal of Medical Entomology 9:439-442.

Hair, J. A., W. J. Gladhey, R. B. Davey, R. O. Drummond, and P. D. Teel. 1979. Sustained-release famphur bolus for control of *Boophilus* ticks. Journal of Economic Entomology 72:135-138.

Heath, A. C. G. J. D. Tenquist, and D. M. Bishop. 1980. Effects of pour-on organophosphate insecticides and a diamidide acaricide on the cattle tick, *Haemaphysalis longicornis*. New Zealand Journal of Experimental Agriculture 8:79-81.

Heinz, G. H., E. F. Hill, W. H. Stickel, and L. F. Stickel. 1979. Environmental contaminant studies by the Patuxent Wildlife Research Center. Pages 9-35 *in* E. E. Kenaga, editor. Avian and mammalian wildlife toxicology. American Society for Testing and Materials Special Technical Publication 693, Philadelphia, Pa.

Henny, C. J., L. J. Blus, E. J. Kolbe, and R. E. Fitzner. 1985. Organophosphate insecticide (famphur) topically applied to cattle kills magpies and hawks. Journal of Wildlife Management 49:648-658.

Henny, C. J., E. J. Kolbe, E. F. Hill, and L. J. Blus. 1987. Case histories of bald eagles and other raptors killed by organophosphorus insecticides topically applied to livestock. Journal of Wildlife Diseases 23:292-295.

Hill, E. F. 1992. Avian toxicology of anticholinesterases. Pages 272-294 *in* B. Ballantyne and T. C. Marrs, editors. Clinical and experimental toxicology of organophosphates and carbamates. Butterworth-Heinemann, Oxford, England.

Hill, E. F., and M. B. Camardese. 1986. Lethal dietary toxicities of environmental contaminants and pesticides to coturnix. U.S. Fish and Wildlife Service Technical Report 2. 147 pp.

Hill, E. F., R. G. Heath, J. W. Spann, and J. D. Williams. 1975. Lethal dietary toxicities of environmental pollutants to birds. U.S. Fish and Wildlife Service Special Scientific Report--Wildlife 191. 61 pp.

Hill, E. F., and V. M. Mendenhall. 1980. Secondary poisoning of barn owls with famphur, an organophosphate insecticide. Journal of Wildlife Management 44:676-681.

Hudson, R. H., R.K. Tucker, and M. A. Haegele. 1984. Handbook of toxicity of pesticides to wildlife. Second edition. U.S. Fish and Wildlife Service Resource Publication 153.90 pp.

Ivey, M. C. J. S. Palmer, and R. H. Washburn. 1976. Famphur and its oxygen analogue: residues in the body tissues of reindeer. Journal of Economic Entomology 69:260-262.

Johnson, W. P., B. T. Alford, and J. J. Drain. 1972. Safety of famphur to young Brahman heifers, bulls and steers. Veterinary Medicine, Small Animal Clinician 67:686.

Kaemmerer, K., and S. Buntenkotter. 1973. The problem of residues in meat of edible domestic animals after application or intake of organophosphate esters. Residue Reviews 46:1-240.

Khan, M. A., and G. C. Kozub. 1981. Systemic control of cattle grubs (*Hypoderma* spp.) in steers treated with Warbex and weight gains associated with grub control. Canadian Journal of Comparative Medicine 45:15-19.

Khan, M. A. Q., editor. 1977. Pesticides in aquatic environments. Plenum Press, New York. 257 pp.

Loomis, E. C., and R. C. Schock. 1978. Comparison of famphur (warbex) pour-on and intramuscular injectable formulations for cattle grub control, California, 1975-1976. Journal of Medical Entomology 14:649-651.

Mineau, P., editor. 1991. Cholinesterase-inhibiting insecticides. Their impact on wildlife and the environment. Chemicals in agriculture. Volume 2. Elsevier Science Publishers, Amsterdam, The Netherlands. 348 pp.

Negherbon, W. O. 1959. Organic phosphates. Pages 536-576 *in* W. O. Negherbon, editor. Handbook of toxicology. Volume III. Insecticides. A compendium. WADC Technical Report 55-16. Aero Medical Laboratory, Wright Air Development Center, Air Research and Development Command, U.S. Air Force, Wright-Patterson Air Force Base, Ohio. Armed Services Technical Information Agency. Arlington Hall Station, Va.

Nieminen, M., J. Timisjarvi, and M. Laitinen. 1980. The effects of antiparasitic treatment on the condition of semi-domestic reindeer (*Rangifer tarandus*). Reports from the Kevo Subarctic Research Station (Finland) 16:23-26.

Nordkvist, M. 1975. Large scale field trials against larvae of *Oedemagena tarandi* and *Cephenomyia trompe* in Swedish reindeer. Biological Papers of the University of Alaska 1 :518-522.

O'Brien, R. D., and C. E. Dannelley. 1965. Penetration of insecticides through rat skin. Journal of Agricultural and Food Chemistry 13:245-247.

O'Brien, R. D., E. C. Kimmel, and P. R. Sferra. 1965. Toxicity and metabolism of famphur in insects and mice. Journal of Agricultural and Food Chemistry 13:366-369.

Pasarela, N. R., R. E. Tondreau, W. R. Bohn, and G. O. Gale. 1967. Gas chromatographic determination of famphur and its oxygen analog residues in bovine milk, blood, and edible tissues. Journal of Agricultural and Food Chemistry 15:920-926.

Powell, G. V. N., and D.C. Gray. 1980. Dosing free-living nestling starlings with an organophosphate pesticide, famphur. Journal of Wildlife Management 44:918-921.

Randell, W. F., and R. E. Bradley. 1980. Effects of injectable famphur on young Brahman and Angus cattle. American Journal of Veterinary Research 44:1423-1426.

Ryan, J. J., and H. A. McLeod. 1979. Chemical methods for the analysis of veterinary drug residues in foods. Part I. Residue Reviews 71:1-82.

Schafer, E. W. 1972. The acute oral toxicity of 369 pesticidal, pharmaceutical and other chemicals to wild birds. Toxicology and Applied Pharmacology 21:315-330.

Seel, D.C. 1985. Magpie containing warble-fly insecticide. British Birds 78:302-303.

Sine, C., editor. 1991. Farm Chemicals Handbook '91. Meister Publishing Company, Willoughby, Ohio.

Smith, G. J. 1987. Pesticide use and toxicology in relation to wildlife: organophosphorus and carbamate compounds. U.S. Fish and Wildlife Service Resource Publication 170. 171 pp.

Smith, H. G, Jr., and R. L. Goulding. 1970. Toxicological aspects of three organophosphorus compounds (cythioate, famphur, and fenthion) in the host-ectoparasite system. Journal of Economic Entomology 63:1640-1646.

Tarry, D. W. 1986. Progress in warble fly eradication. Parasitology Today 2:111-116.

Teel, P. D., J. A. Hair, and T. C. Randolph, Jr. 1977. Continuous administration of famphur for control of ticks and bed bugs feeding on ruminants. Journal of Economic Entomology 70:664-666.

Teel, P. D., J. A. Hair, and L. G. Stratton. 1979. Laboratory evaluation of a sustained-release famphur bolus against Gulf coast and lone star ticks feeding on Hereford heifers. Journal of Economic Entomology 72:230-233.

Tucker, R. K., and D. G. Crabtree. 1970. Handbook of toxicity of pesticides to wildlife. U.S. Fish and Wild-life Service Resource Publication 84. 131 pp.

Vaughan, J., and E. C. Turner, Jr. 1984. Residual and topical toxicity of various insecticides to the lesser mealworm (Coleoptera:Tenebrionidae). Journal of Economic Entomology 77:216-220.

Watson, K., and W. D. Black. 1981. Whole blood cholinesterase activity in calves after topical treatment with famphur. Canadian Veterinary Journal 22:179-181.

White, D. H., L. E. Hayes, and P. B. Bush. 1989. Case histories of wild birds killed intentionally with famphur in Georgia and West Virginia. Journal of Wildlife Diseases 25: 184-188.

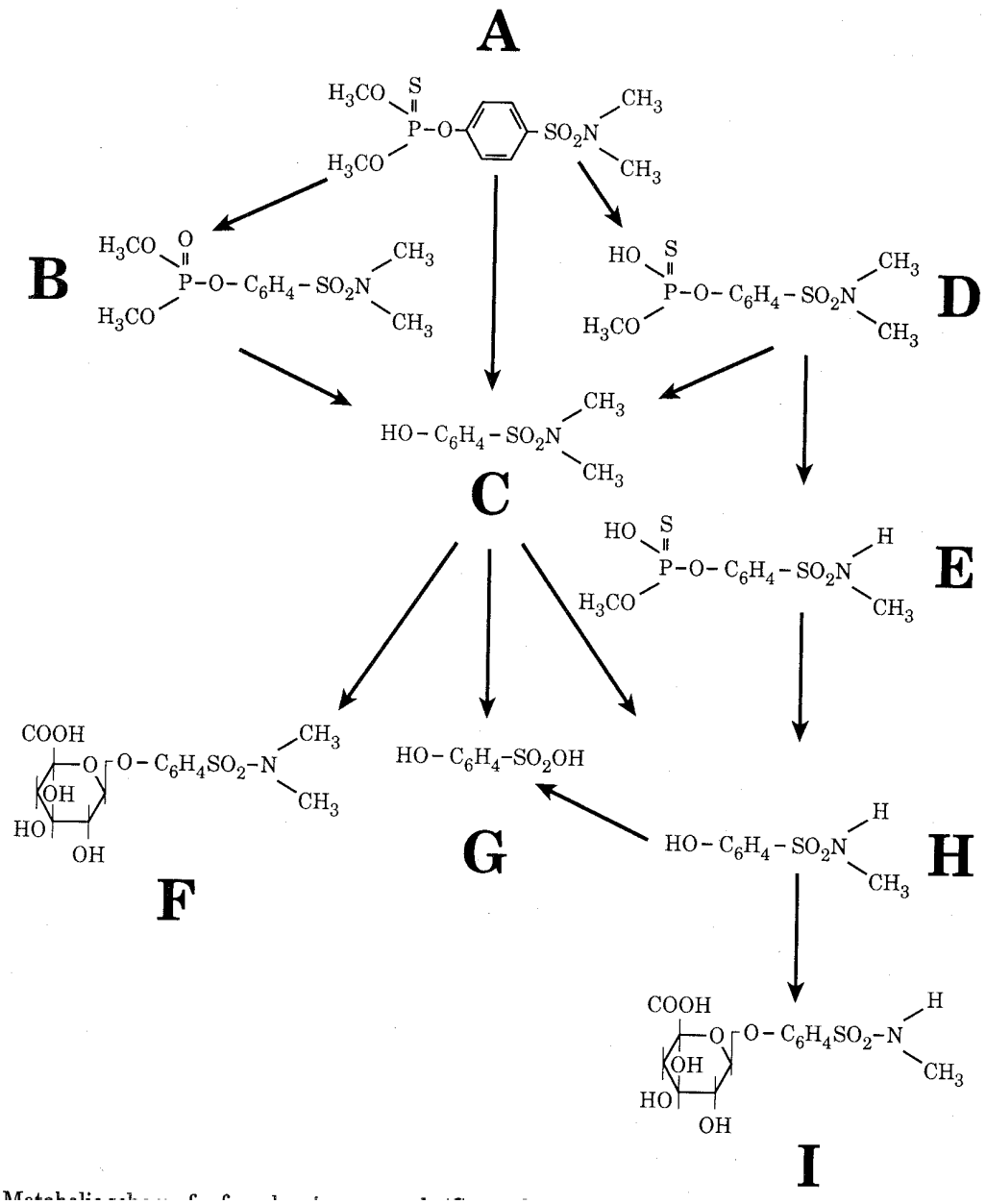

Figure. Metabolic scheme for famphur in mammals (Gatterdam et al. 1967). Major metabolic routes are indicated by an asterisk (*). A, famphur; B, famoxon; C, *p*-(N,N-dimethylsulfamoyl)phenol; D, *O*-desmethylfamphur; E, *O*, N-bisdesmethylfamphur; F, *p*-(N,N-dimethylsulfamoyl)phenyl glucuronide; G, *p*-hydroxybenzene sulfonic acid; H, *p*-(N-methylsulfamoyl)phenol; and I, *p*-(N-methylsulfamoyl)phenyl glucuronide. According to this scheme, famphur (A) initially undergoes oxidation at the P=S bond to yield famoxon (B), or hydrolysis at the P-*O*-phenyl bond to yield the transitory *p*-(N,N-dimethylsulfamoyl)phenol (C)*, or hydrolysis at one of the P-*O*-methyl bonds to yield *O*-desmethylfamphur (D)*. *p*, N,N-dimethylsulfamoyl)phenol (C) may also arise by hydrolysis of famoxon (B) or *O*-desmethylfamphur (D)*. p-(N,N-dimethylsulfamoyl)phenol (C) is immediately conjugated to fore *p*-(N,N-dimethylsulfamoyl)phenyl glucoronide (F)*, or transformed to *p*-hydroxybenzene sulfonic acid (G) or *p*-(N-methylsulfamoyl)phenol (H). *O*-desmethylfamphur (D) can also give rise to *O*, N-bisdesmethylfamphur (E)* by removal of one of the methyl groups of the sulfonamide moiety. *O*, N-bisdesmethylfamphur (E) is hydrolyzed to the corresponding transitory *p*-(N-methylsulfamoylphenol) (H)* which is immediately conjugated to yield the corresponding glucoronide, *p*-(N-methylsulfamoyl)phenyl glucuronide (I)*.