Distribution and Tissue Elimination in Rats during and after Prolonged Dietary Exposure to a Highly Fluorinated Sulfonamide Pesticide

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Rats were fed either nonfortified, ground rodent feed or feed fortified with 75 mg of sulfluramid/kg of feed for 56 days and then were fed the nonfortified diet for an additional 35 days. Samples from nine tissues and blood samples were collected and analyzed by gas chromatography. No overt clinical signs of toxicity were observed during the study except for a significant decrease in body weight gained in the treated group compared to the controls. This difference appeared to result from a significant reduction in rate of weight gain during the first 2 weeks of treatment. Diet consumption was not significantly different for treated and control groups. There were no detectable levels of sulfluramid present in tissue or blood samples during the study, but its metabolite, deethylsulfluramid, was present, and changes in its concentration were associated with first-order elimination kinetics. The blood half-life of 10.8 days was greater than those for the solid tissues. The half-life for fat was 1.1 days. Though highly lipid soluble, neither sulfluramid nor deethylsulfluramid accumulated in the tissues of the rats during the 56-day dosing period.

INTRODUCTION

Sulfluramid (*N*-ethylperfluorooctanesulfonamide, GX-071) has been approved for use as a household ant and roach bait (Raid Max, Johnson and Son, Racine, WI). The chemical formula of sulfluramid (Figure 1) is $CF_3(CF_2)_7SO_2NHC_2H_5$. The long fluoride chain makes the compound unique among polyhaloalkanes. The ability of sulfluramid to control the red imported fire ant (*Solenopsis invicta* Buren) has been demonstrated (Vander Meer et al., 1986; Williams et al., 1987). Consideration of sulfluramid for use on agricultural lands requires toxicokinetic studies to assess the potential for accumulation in the tissues of exposed animals (U.S. Environmental Protection Agency, 1982a,b, 1984).

Gas chromatographic and mass spectra analyses of blood from dogs and rats dosed with sulfluramid have identified the major metabolite in these species as perfluorooctanesulfonamide or deethylsulfluramid (Figure 1), the N-deethylated form of sulfluramid (Arrendale et al., 1989a). Manning et al. (1990) administered [^{14}C-*ethyl*]sulfluramid to rats in a single bolus by gavage to evaluate the metabolism and disposition of sulfluramid. The results of this study provided additional evidence for a deethylation reaction in the metabolism of sulfluramid. However, this study did not measure actual concentration of deethylsulfluramid in tissues. Deethylsulfluramid is probably responsible for the toxicological effects associated with exposure to sulfluramid. Schnellmann (1990) and Schnellmann and Manning (1990) have shown that deethylsulfluramid is able to uncouple oxidative phosphorylation in renal proximal tubules and isolated renal cortical mitochondria, respectively.

The purposes of the present study were (1) to determine the potential for bioaccumulation in animals consuming a nonlethal level of sulfluramid in the diet for 56 days, (2) to evaluate the distribution and tissue elimination of deethylsulfluramid, and (3) to compare the tissue and blood kinetics to determine whether blood kinetics can serve to accurately predict the tissue kinetics for this compound.

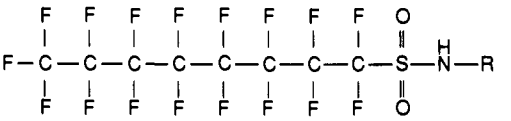

Figure 1. Structure of sulfluramid (R = C_2H_5) (molecular weight = 527) and deethylsulfluramid (R = H).

METHODS AND MATERIALS

Experimental Design. Sprague-Dawley male rats (age 32–35 days; mean body weight 99.3 g) were obtained from Harlan Laboratories. The rats were quarantined for 7 days and allowed to acclimate to consumption of ground (mesh size 2 mm) rodent feed (Wayne MRH 22/5 Rodent Blox, Madison, WI) from feeder jars. Animals were housed individually in stainless steel wire mesh cages. The animal room was maintained at 25 °C and had a 12-h light/dark cycle. The rats were randomly divided into 10 groups, each consisting of 5 treated and 1 control animal. Prior to treatment initiation, all rats exhibited normal weight gain for their sex and age (Altman, 1972).

During the treatment phase, the treated rats of all 10 study groups were placed on a diet consisting of the ground feed fortified with sulfluramid at a concentration of 75 mg of sulfluramid/kg of feed. The control rats were fed nonfortified, ground feed. Weekly body weight and feed consumption records were maintained throughout the study. On days 7, 14, 28, 42, and 56 of the treatment phase, one group was euthanatized using carbon dioxide. During the semicomatose phase, 2 mL of blood was collected from each animal via cardiac puncture. The blood samples were refrigerated in NaEDTA tubes. After euthanasia, tissues were immediately collected and included peritesticular fat, skeletal muscle (biceps femoris), testes, liver, kidney, spleen, heart, lung, and brain. Except for fat samples, each 0.5-g tissue sample was then prepared for extraction on the day of collection and analyzed for sulfluramid and deethylsulfluramid as described below. Fat samples were stored frozen (−20 °C) for later analysis.

After 56 treatment days, the remaining five treatment groups were transferred to the ground control diet for the recovery or posttreatment phase. To evaluate the elimination of deethylsulfluramid and sulfluramid, one group consisting of five exposed rats and one control rat was sacrificed on days 7, 10, 17, 24, and 35 of the posttreatment phase for collection and analyses of the same tissue and blood samples as described above.

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Diet. Fresh feed was fortified every 2–3 weeks to avoid any possibility of a significant decrease in feed concentration of sulfluramid. The feed was fortified by adding 1.5 g of sulfluramid in 150 mL of acetone to 20 kg of ground rodent feed while blending thoroughly for 13 min in a mixer. The acetone was allowed to evaporate from the feed for 24 h prior to feeding. To verify the homogeneity, stability, and final concentration of sulfluramid, the feed was assayed weekly. Five randomly collected 2-g samples of the fortified feed were placed into 50-mL culture tubes with Teflon-lined screw caps. After 10 mL of Optima GC grade ethyl acetate (Fisher Scientific, West Haven, CT) was added to each sample, the tubes were vortexed and then centrifuged at 1100*g* for 30 min. The concentration of sulfluramid was quantitated by gas chromatography as described by Arrendale et al. (1989b).

Enzyme Tissue Digestion. Tissue extraction of sulfluramid and deethylsulfluramid was carried out using a procedure based on enzyme digestion of tissue as described by de Groot and Wubs (1987) with the exception that a higher collagenase concentration was used. Each tissue sample was minced with a scalpel blade and placed into a 50-mL centrifugation tube with a Teflon-lined screw cap. To each sample was added 3 mL of the enzyme solution (prepared fresh prior to each extraction). The concentrations of the enzymes were 900 IU of collagenase/mL (*Clostridium histolyticum*, type 1A; Sigma Chemical Co., St. Louis, MO) and 21 IU of protease/mL (subtilisin Carlsberg, type VIII; Sigma) in deionized water. For fat digestion, the enzyme lipase (triacylglycerol lipase, type II, Sigma) was added to the enzyme solution to provide a concentration of 30 IU/mL. To retard bacterial and fungal growth during the incubation period, 50 μL of an antibiotic/antifungal solution was added to each sample. The solution contained amphotericin B (10 μg/mL), penicillin (5000 IU/mL), and streptomycin (5.0 mg/mL). The samples were vortexed and placed into a 37 °C incubator for 12 h. After 6 h of incubation, each sample was vortexed to aid the digestion of the tissue. At 12 h, the tissue was vortexed once more and visually inspected to ensure that tissue digestion was complete prior to extraction.

Incubation of sulfluramid and deethylsulfluramid with the enzyme mixture for up to 72 h at 37 °C did not alter the concentrations of these compounds.

Extraction. After 10 mL of EtAc was added to each tissue sample mixture, the tubes were vortexed three times for 15 s each. The samples were allowed to stand for 3 min between each vortexing. Samples were then centrifuged at 1100*g* for 20 min, and an aliquot of the clear supernatant was removed and placed into a 2-mL crimp-top autosampler vial for analysis.

Heparinized blood (0.5 mL) was placed in a 10-mL test tube with Teflon-lined screw cap, and then 5 mL of EtAc was added. The samples were vortexed and then centrifuged at 560*g* for 8 min. An aliquot of the supernatant was removed and placed into a 2-mL crimp-top autosampler vial for analyses.

Analyses. Tissue and blood samples were analyzed with an HP gas chromatograph (Model 5890, Hewlett-Packard, Avondale, PA) equipped with an electron capture detector, HP automatic sampler (Model 7673A), and HP integrator (Model 3392A). A 15 m × 0.53 mm (i.d.) fused silica megabore capillary column with a film thickness of 1.0 μm was used (Durabond-Wax; J&W Scientific, Folsum, CA). The temperature program of the gas chromatograph was as follows: injection port, 200 °C; detector, 300 °C; initial column temperature, 60 °C; from 60 to 120 °C at 30 °C/min; from 120 to 220 °C at 12 °C/min; hold at 220 °C for 5 min. The column flow rate was 20 mL/min (He), and the detector makeup flow rate was 40 mL/min (N_2). Injections of 1 μL were made in the splitless mode (purge on at time = 30 s). Chromatograms have been published (Arrendale et al., 1989a,b; Manning et al., 1991). Fat samples were handled in a similar manner except that a 30 m × 0.32 mm (i.d.) fused silica capillary column with a film thickness of 1.0 μm was used to improve separation of contaminant peaks from the deethylsulfluramid peak (Durabond-5; J&W Scientific). The temperature program of the gas chromatograph was as follows: injection port, 200 °C; detector, 300 °C; initial column temperature, 65 °C; from 65 to 200 °C at 12 °C/min; from 200 to 300 °C at 30 °C/min; hold at 300 °C for 5 min. Flow rates and injection volume were the same as described above.

External standards of sulfluramid and deethylsulfluramid were prepared in acetone prior to the study and stored in brown glass bottles at 4 °C. Sulfluramid (99.9% purity) and deethylsulfluramid (>95% purity) were supplied by the Griffin Corp., Valdosta, GA. Periodically throughout the study, these standards were checked against freshly prepared standards to ensure stability. A set of standards was evaluated before and during each set of study samples. A regression analysis was conducted on each set of external standards to determine linearity. A correlation coefficient greater than 0.998 was routinely obtained. Tests with fortified blood and tissue samples yielded extraction efficiencies of 83–127% in the concentration range encountered in this study. Recoveries exceeding 100% were associated with concentrations approaching the detection limits. The method detection limit (MDL) for sulfluramid was 0.22 μg/g and for deethylsulfluramid, 0.31 μg/g. The MDL was calculated using the confidence limit method described by Hubaux and Vox (1970).

Statistics. A multifactor ANOVA was used to assess the significant differences in weight gain and feed consumption between control and treatment groups. A multifactor ANOVA also was used to determine significant differences within the selected tissues after steady-state concentration was reached during the 8 weeks on the sulfluramid-fortified diet. Multiple means comparisons of body weights were done using Tukey's and LSD tests. A pharmacokinetics software package (Fox and Lamson, 1986) was used to evaluate tissue concentration vs time profile for calculation of the tissue elimination half-lives ($T_{1/2}$). All data are reported as mean ± SD. Statistical significance was set at $p \leq 0.05$.

Table I. Stability of Sulfluramid in Fortified Rodent Feed

batch[a]	week[b]	mean[c]	CV[d]
1	0	71.0	1.67
	1	72.1	1.74
	2	70.4	2.65
	3	70.3	1.36
2	0	72.2	1.19
	1	72.7	1.49
	2	69.2	2.47
3	0	71.2	0.78
	1	72.5	2.34
	2	70.2	1.80

[a] Each batch of feed was fortified with 75 mg/kg of sulfluramid. [b] Time after fortifying feed. [c] Mean (mg/kg) of five samples. [d] Coefficient of variation (%).

Table II. Mean Weekly Diet Consumption per Kilogram of Body Weight of Rats

	control			treated		
week	mean, g	SD	*n*	mean, g	SD	*n*
0[a]	764.9	36.1	10	735.2	60.4	50
1[b]	700.5	61.0	10	665.3	67.1	50
2[b]	649.3	32.0	9	634.9	64.0	45
3	545.8	40.2	8	556.3	45.6	40
4[b]	526.8	41.7	8	541.6	68.5	40
5	520.0	29.1	7	540.6	57.9	35
6[b]	472.2	18.0	7	520.5	48.6	35
7	497.4	21.8	6	508.8	51.1	30
8[b]	438.3	31.3	6	483.9	57.0	30

[a] Acclimation period. [b] Rats were sacrificed at the ends of these weeks.

RESULTS

The mean assayed concentration (71.0 ± 0.8 mg/kg of diet) of sulfluramid was about 5% below the amount added but appeared to be stable during the 2- or 3-week period of feeding the diet and between batches of diet (Table I). The low coefficient of variation for the assay results indicated homogeneity of distribution of sulfluramid in the diet. No significant difference in the diet consumption between the control and treatment groups was noted during the 56-day exposure period (Table II). The mean daily sulfluramid consumption was 6.6 ± 0.5 mg/kg during the initial rapid growth period of the rats, which decreased to 4.9 ± 0.5 mg/kg as the rats matured (Figure 2). This

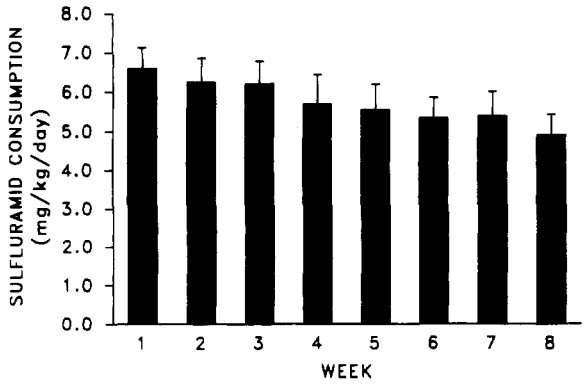

Figure 2. Total weekly pesticide consumption (mean ± SD) in treated rats during the 8-week exposure to the sulfluramid-fortified diet.

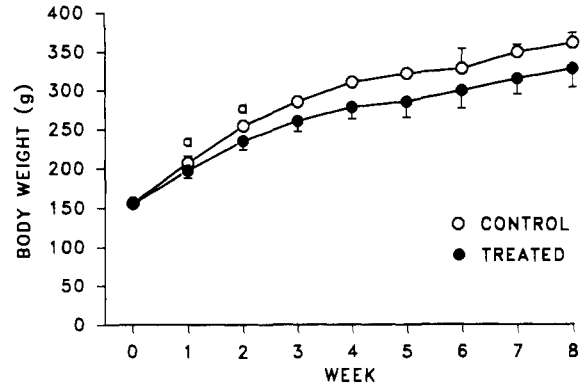

Figure 3. Weekly weights (mean ± SD) for control rats and rats on the sulfluramid-fortified diet. The weekly periods during which there was a significant difference in rate of weight gain between the treated and control rats are designated by the letter a. There was a significant difference in body weights between treated and control rats from week 1 through week 8. SDs not exceeding the size of the symbol are omitted.

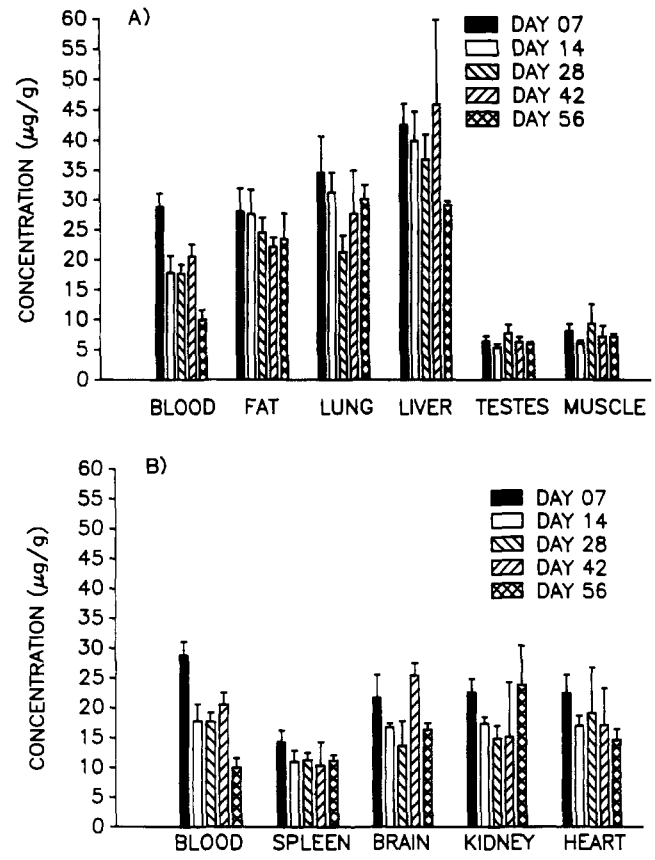

Figure 4. Concentration (mean ± SD) of deethylsulfluramid in tissues of rats consuming sulfluramid-fortified diet. (A) Levels in liver and lung were significantly greater than in blood. Levels in testes and muscle were significantly less than in blood. (B) The concentrations in these tissues were not significantly different from those in blood.

decrease was associated with a slowing of the rate of increase in diet consumption as the rats matured. The mean daily consumption for the 56-day dosing period was 5.7 ± 0.6 mg/kg.

There was a significant difference ($p < 0.01$) in body weights between control and treated rats each week while on the fortified diet (Figure 3). During the latter half of the treatment period, the treated rats weighed about 9.6% less than the control rats. There was a significant decrease in rate of growth of the treated rats during the first and the second weeks of treatment. Rates of gain for control rats for weeks 1 and 2 were 50.7 ± 13.4 and 47.7 ± 8.1 g/week, respectively, and for treated rats, 42.2 ± 7.3 and 38.0 ± 8.6 g/week, respectively. No overt clinical signs of toxicity such as lethargy, increased respiratory and heart rates, hyperexcitability, or convulsions were displayed by any of the treated rats throughout the course of the study with the exception of the early decrease in rate of weight gain in treated rats compared to controls and the body weight differences. Results for body weight during the elimination period suggested that differences between the groups narrowed, but the small number of control rats remaining during this period precluded statistical analysis.

No detectable levels of sulfluramid appeared in the tissue or blood samples examined during the study. However, deethylsulfluramid, the major metabolite of sulfluramid, was detected in all tissues and blood collected at the first sampling time (day 7) and thereafter while the rats were on the fortified diet (Figure 4).

A relatively steady-state concentration (C_{ss}) of deethylsulfluramid was attained in all tissues sampled by day 7 on the sulfluramid diet, and while somewhat variable, the concentration variations lack significant upward or downward trends through day 56 except for blood. The deethylsulfluramid concentration in the blood between day 42 (20.5 ± 2.0 μg/g) and day 56 (9.9 ± 1.6 μg/g) differed significantly (Figure 4). Because of this difference, the mean of all five collection times (days 7, 14, 28, 42, and 56) was used to calculate the C_{ss} for blood, while the concentration at day 56 was used for the C_{ss} for the other tissues. Also, the deethylsulfluramid concentration in liver was significantly lower at day 56 than at day 7, but the difference was not as large as that for this difference in blood. Kidney was the only tissue having a higher concentration at day 56 than at day 7, but the difference was not significant. Only brain and liver had higher concentrations at day 42 than at day 7, but the differences were not significant.

Deethylsulfluramid concentrations at day 56 were highest in fat (23.4 ± 4.2 μg/g), lung (30.1 ± 2.4 μg/g), and liver (29.1 ± 0.7 μg/g) (Figure 4A). The lowest concentrations were found in the testes (5.9 ± 0.3 μg/g) and skeletal muscle (7.1 ± 0.5 μg/g) (Figure 4A). The concentrations in the fat, lung, and liver were higher than the mean concentration for blood (18.5 ± 1.6 μg/g), and the concentrations in the testes and muscle were significantly lower than in blood (Figure 4A). The remaining tissues analyzed (spleen, brain, kidney, and heart) did not have concentrations of deethylsulfluramid significantly different from that in blood (Figure 4B).

In vivo tissue/blood partition ratios were determined for deethylsulfluramid (Table III). Liver and lung had the highest tissue/blood partition ratios at 1.54 ± 0.02 and 1.59 ± 0.05, respectively. Muscle and testes had the lowest partition ratios at 0.30 ± 0.19 and 0.38 ± 0.22, respectively.

Table III. Deethylsulfluramid Tissue/Blood Partition Ratio[a]

tissue/blood	ratio[b]	tissue/blood	ratio[b]
lung/blood	1.59 ± 0.05	heart/blood	0.77 ± 0.18
liver/blood	1.54 ± 0.02	spleen/blood	0.59 ± 0.16
fat/blood	1.32 ± 0.08	testes/blood	0.38 ± 0.22
kidney/blood	1.25 ± 0.25	muscle/blood	0.30 ± 0.19
brain/blood	0.86 ± 0.09		

[a] Based on concentrations of deethylsulfluramid reached on day 7 on the fortified diet. [b] Mean ± SD.

Table IV. Elimination Half-Life[a] of Deethylsulfluramid in Selected Tissues and Tissue Residues at Day 35 Postexposure

tissue	$T_{1/2}$, days	at day 35, μg/g
blood	10.8[b]	3.00
liver	6.9	3.80
spleen	5.5	1.58
kidney	5.4	2.00
heart	4.5	0.87
lung	4.4	2.70
brain	2.6	0.36
fat	1.1	<0.31
muscle	ND[c]	<0.31
testes	ND[c]	<0.31

[a] Analyzed from steady-state concentration to 35 days postexposure concentration by RSTRIP pharmacokinetics software. [b] Standard deviations could not be determined as each set of rats was euthanized at each sampling time. [c] Not determined because concentrations were below the method detection limit (0.31 μg/g) at most of the postexposure sampling times.

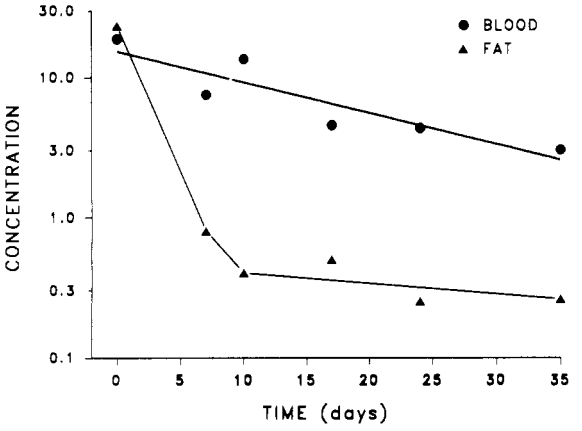

Figure 5. Elimination of deethylsulfluramid from blood (μg/mL) and fat (μg/g). The initial concentrations (day 0) are based on results obtained prior to placing the treated rats on the sulfluramid-free diet. A regression line is used to describe the trend in the blood concentration. The line for fat is estimated because results for the last two points were of limited accuracy since they were below the method detection limit for deethylsulfluramid.

All tissue elimination curves for deethylsulfluramid were best fit by monoexponential linear analysis or first-order elimination kinetics for a one-compartment system with the exception of fat. The data for fat were best fit by biexponential analysis for a two-compartment model which provided two $T_{1/2}$ values (1.1 days; 34.4 days) (Table IV). However, the accuracy of this analysis is questionable because the initial rapid elimination (days 0–7) lacked sufficient points and the subsequent values were very close to or below the method detection limit (0.31 μg/g) for deethylsulfluramid (Figure 5). The deethylsulfluramid elimination half-life in blood was 10.8 days, which was longer than for any of the other tissues (Table IV). Tissue residues of deethylsulfluramid at the last postexposure sampling time (35 days) were above the method detection limit (0.31 μg/g) for all tissues except fat, muscle, and testes (Table IV).

DISCUSSION

Signs of toxicity in rats resulting from consumption of a diet fortified with sulfluramid (150 mg/kg) included lethargy, increased respiratory and heart rates, hyperexcitability, and convulsions (W. L. Chapman, 1988, GX-071 90-day subchronic oral toxicity study in rats, unpublished study, University of Georgia, personal communication). The concentration of sulfluramid selected for use in the diet in this study was half (75 mg/kg) that used in the previous study and was intended to minimize clinical toxicity while permitting focus on the kinetics of this highly fluorinated sulfonamide and its metabolite, particularly as it pertains to understanding their potential for producing tissue residues. The only sign of toxicity noted from daily consumption of a mean concentration of sulfluramid of 5.7 ± 0.6 mg/kg for 56 days was a significant difference in the rate of weight gain of treated rats compared to control rats during the first 2 weeks on the fortified diet (Figure 3). This transitory alteration in the rate of weight gain appeared to result in a significant difference ($p < 0.01$) in body weights over the 8-week exposure to sulfluramid.

The absence of sulfluramid at the first sampling time and thereafter is consistent with previous studies (Arrendale et al., 1989a; Manning et al., 1991), which indicated that sulfluramid is rapidly metabolized to deethylsulfluramid after oral administration, most likely by "first pass" hepatic metabolism, but the intestinal mucosa and gastrointestinal flora may play a role (Tesoriero and Roxon, 1975; Walters and Combes, 1985). This rapid conversion to deethylsulfluramid suggests that the decreased body weight associated with the consumption of sulfluramid was caused by deethylsulfluramid, possibly through its ability to uncouple oxidative phosphorylation since diet consumption was similar for the two groups (Schnellmann, 1990; Schnellmann and Manning, 1990). Despite the differences in the rate of weight gain noted above, the treated rats appeared to be able to adapt to the effects of deethylsulfluramid at this concentration as rate of gain was similar to that of controls for subsequent weeks. However, the treated rats did not recover from the retardation in body weight during the treatment period, although the results for the elimination period suggested that the difference between the two groups was decreasing. Rate of elimination of deethylsulfluramid does not appear to be limited by the rate of metabolism of the parent compound, sulfluramid, which is very rapid, but in the presence of liver disease, some effect might be expected.

Deethylsulfluramid attained a relatively steady-state concentration or peak concentration in all tissues within 7 days, even though exposure continued for an additional 49 days. Liver, lung, and fat had the highest affinity for deethylsulfluramid, while muscle and testes had the lowest affinity, based on the tissue/blood partition ratios (Table III). The partition ratios for deethylsulfluramid are of special interest when contrasted with those for a compound such as diisopropyl fluorophosphate (DFP) (Gearhart et al., 1990). For DFP the partition ratios were similar for liver (1.56) and brain (0.67) to those for deethylsulfluramid, but the fat partition ratio for DFP was much higher (17.6) than that for deethylsulfluramid (1.32).

The log values for the octanol/water partition coefficient (log P) for sulfluramid and deethylsulfluramid are greater than 6.85 and 4.5, respectively, on the basis of experiments in our laboratory and at Griffin Corp. The increased polarity of the metabolite very likely accounts for its decrease in lipophilicity. Generally, a log P greater than 2.5 indicates a compound could be stored in adipose tissue (Bickel, 1984). All polyhalogenated compounds are highly

lipophilic and have log P values equal to or greater than 4.5, e.g., log P for DDT is 5.9 (Bickel, 1984). DDT is especially well-known for its ability to steadily accumulate in adipose tissues of exposed animals (Sharma et al., 1979). However, a high log P does not assure fat accumulation of a compound as indicated by the results for deethylsulfluramid, which did not accumulate in fat. This is probably related to its not having a high affinity for binding to adipose tissue, as suggested by Bickel (1984) for other lipophilic compounds.

The accumulation ratio is used to describe the tendency of a compound to accumulate in adipose tissue (Onley et al., 1975). It is calculated on the basis of the concentration ratio of a compound in adipose tissue to that in feed. The accumulation ratio for the organochlorine compound dieldrin in chickens is 15 and that for DDT is 9, while that for the DDT metabolite DDE is 3 compared to the level of its parent compound in feed. In the present study the accumulation ratio for deethylsulfluramid was 0.3, which provides additional evidence for the low affinity of this compound for fat.

Although the concentration in the fat was initially somewhat higher than that in blood, the level in fat rapidly declined as the compound left the fat and entered the systemic circulation (Figure 5). Under these conditions, the relatively long blood $T_{1/2}$ may be related to deethylsulfluramid being released from tissues into the blood. Other factors effecting the longer blood $T_{1/2}$ of deethylsulfluramid could include high specific binding affinity for plasma proteins or hemoglobin and continued enterohepatic circulation. Blood $T_{1/2}$ values are longer than fat $T_{1/2}$ values for other compounds also. For example, the blood $T_{1/2}$ for DDE in the rat is 217 days while that for fat is 48 days (Bickel, 1984).

The fact that blood had the longest $T_{1/2}$ of the tissues evaluated suggested that when the concentration in blood is below the method detection limit, it would also be below the detection limit in all of the other tissues examined (Table III). Therefore, while blood and tissue kinetic data are needed to completely describe the dynamics of a compound, the results of this study suggest that blood kinetics alone should suffice in predicting elimination of this compound from the body of the rat.

Because of its high lipid solubility and molecular weight (499), it appears likely that deethylsulfluramid may be eliminated in the bile, as are other compounds with similar characteristics (Millburn et al., 1967). This would also support the theory of an enterohepatic circulation type metabolism for deethylsulfluramid.

Because of the possible widespread commercial use of this unique compound against imported fire ants, an important question is the ability of sulfluramid or deethylsulfluramid to accumulate in the tissues of exposed animals. Since sulfluramid is so rapidly metabolized to deethylsulfluramid, the potential for sulfluramid to bioaccumulate is quite low, at least in the rat. More importantly, the increased polarity and decreased lipid solubility and the associated low affinity for fat and moderate affinity for blood also limit deethylsulfluramid's ability to accumulate in tissues.

ACKNOWLEDGMENT

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LITERATURE CITED

Altman, P. L., Dittmer, D. S., Eds. *Biological Data Book*, 2nd ed.; Federation of American Societies for Experimental Biology: Bethesda, MD, 1972; Vol. 1, p 210.

Arrendale, R. F.; Stewart, J. T.; Manning, R. O.; Vitayavirasuk, B. Determination of GX-071 and its major metabolite in rat blood by cold on-column injection capillary GC/ECD. *J. Agric. Food Chem.* **1989a**, *37*, 1130–1135.

Arrendale, R. F.; Stewart, J. T.; Mispagel, M. E.; Vitayavirasuk, B. Comparison of cold on-column and splitless injection using an automatic liquid sampler: Application to the determination of GX-071 in animal ration. *J. High Resolut. Chromatogr.* **1989b**, *12*, 749–752.

Bickel, M. H. The role of adipose tissue in the distribution and storage of drugs. *Prog. Drug Res.* **1984**, *28*, 273–304.

De Groot, G.; Wubs, K. L. A simple enzymic digestion procedure of intact tissue samples in pharmacokinetics drug analysis. *J. Appl. Toxicol.* **1987**, *11*, 175–179.

Fox, J. L.; Lamson, M. L. *RSTRIP User Handbook*; Micromath Scientific Software: Salt Lake City, 1986; pp 1–62.

Gearhart, J. M.; Jepson, G. W.; Clewell, H. J.; Andersen, M. E.; Conolly, R. B. Physiologically based pharmacokinetic and pharmacodynamic model for the inhibition of acetylcholinesterase by diisopropylfluorophosphate. *Toxicol. Appl. Pharmacol.* **1990**, *106*, 295–310.

Hubaux, A.; Vos, G. Decision and detection limits for linear calibration curves. *Anal. Chem.* **1970**, *42*, 849–855.

Manning, R. O.; Bruckner, J. V.; Mispagel, M. E.; Bowen, J. M. Metabolism and disposition of sulfluramid, a unique polyfluorinated insecticide, in the rat. *Drug Metab. Dispos.* **1991**, *19*, 205–211.

Millburn, P.; Smith, R. L.; Williams, R. T. Biliary excretion of foreign compounds—Biphenyl, stilboestrol, and phenolphthalein in the rat: Molecular weight, polarity, and metabolism as factors in biliary excretion. *Biochem. J.* **1967**, *105*, 1275–1281.

Onley, J. H.; Giuffrida, L.; Watts, R. R.; Ives, N. F.; Storhrer, R. W. Residues in broiler chick tissues from low level feeding of seven chlorinated hydrocarbon insecticides. *J. Assoc. Off. Anal. Chem.* **1975**, *58*, 785–792.

Schnellmann, R. G. The mechanism of toxicity of a unique pesticide (N-ethylperfluorooctane sulfonamide) to rabbit renal proximal tubules. *Toxicol. in Vitro* **1990**, *4*, 71–74.

Schnellmann, R. G.; Manning, R. O. Perfluorooctane sulfonamide: A structurally novel uncoupler of oxidative phosphorylation. *Biochim. Biophys. Acta* **1990**, *1016*, 344–348.

Sharma, R. C.; Bhaskan, M.; Bhide, N. K. A simplified chemical method of DDT estimation in the body fat. *Indian J. Exp. Biol.* **1979**, *17*, 1367–1370.

Tesoriero, A. A.; Roxon, J. J. [^{35}S]Cyclamate metabolism: Incorporation of ^{35}S into protein of intestinal bacteria *in vitro* and production of volatile ^{35}S-containing compounds. *Xenobiotica* **1975**, *5*, 25–31.

U.S. Environmental Protection Agency. *Pesticide Assessment Guidelines, Subdivision N. Chemistry: Environmental Fate*; Office of Pesticide Programs (PB83-153973): Washington, DC, Oct 1982a.

U.S. Environmental Protection Agency. *Pesticide Assessment* Guidelines, *Subdivision O: Residue Chemistry*; Office of Pesticide Programs (PB83-153981): Washington, DC, Oct 1982b.

U.S. Environmental Protection Agency. *Pesticide Assessment Guidelines, Subdivision F. Hazard Evaluation: Human and Domestic Animals*; Office of Pesticide Programs (PB86-108958): Washington, DC, Nov 1984.

Vander Meer, R. K.; Lofgren, C. S.; Williams, D. F. Control of *Solenopsis invicta* with delayed-action fluorinated toxicants. *Pestic. Sci.* **1986**, *17*, 449–455.

Walters, J. M.; Combes, R. D. Characterization of a microsomal fraction from rat small intestine for metabolic activation of some promutagens. *Carcinogenesis* **1985**, *6*, 1415–1420.

Williams, D. F.; Lofgren, C. S.; Vander Meer, R. K. The red imported fire ant, *Solenopsis invicta*: Control with fluoroaliphatic sulfluramidone bait toxicants. *J. Agric. Entomol.* **1987**, *4*, 41–47.

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