FUNDAMENTAL AND APPLIED TOXICOLOGY 4, 972–976 (1984)

Cholestyramine-Enhanced Fecal Elimination of Carbon-14 in Rats after Administration of Ammonium [^{14}C]Perfluorooctanoate or Potassium [^{14}C]Perfluorooctanesulfonate

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Cholestyramine-Enhanced Fecal Elimination of Carbon-14 in Rats after Administration of Ammonium [^{14}C]Perfluorooctanoate or Potassium [^{14}C]Perfluorooctanesulfonate. JOHNSON, J. D., GIBSON, S. J., AND OBER, R. E. (1984). *Fundam. Appl. Toxicol.* 4, 972–976. After a single intravenous dose of ammonium [^{14}C]perfluorooctanoate ([^{14}C]PFO, 13.3 mg/kg) or of potassium [^{14}C]perfluorooctanesulfonate ([^{14}C]PFOS, 3.4 mg/kg) to rats, cholestyramine fed daily as a 4% mixture in feed was shown to increase the total carbon-14 eliminated via feces and to decrease liver concentration of carbon-14. Rats were fed cholestyramine in feed for 14 days after administration of [^{14}C]PFO and for 21 days after administration of [^{14}C]PFOS. Control rats were administered radiolabeled fluorochemical but were not treated with cholestyramine. Cholestyramine treatment increased mean cumulative carbon-14 elimination in feces by 9.8-fold for rats administered [^{14}C]PFO and by 9.5-fold for rats administered [^{14}C]PFOS. After [^{14}C]PFO, a mean of 4% of the dose of carbon-14 was in liver of cholestyramine-treated rats at 14 days versus 7.6% in control rats; after [^{14}C]PFOS, 11.3% of the dose was in liver at 21 days versus 40.3% in control rats. After administration of either radiolabeled compound, plasma and red blood cell carbon-14 concentrations, which were relatively lower than liver concentrations, were also significantly reduced by cholestyramine treatment. © 1984 Society of Toxicology.

The anion of perfluorooctanoic acid has been found in the serum of manufacturing plant workers (Ubel *et al.*, 1980). Toxicity studies in animals have been reported (Griffith and Long, 1980). In view of the slow elimination and the presence of the compound in plant workers' serum, a means of enhancing elimination was sought. In addition, since both ammonium perfluorooctanoate and potassium perfluorooctanesulfonate are commercial products and intermediates of products, the possibility of affecting the elimination of perfluorooctanesulfonate was also of interest. Cholestyramine, an agent approved for use in humans to lower cholesterol blood levels, is an anion exchange resin which has been used to promote fecal excretion of the pesticide chlordecone (Kepone) in rats (Cohn *et al.*, 1978). Since both perfluorooctanoic acid and perfluorooctanesulfonic acid are prepared as salts and exist as anions at physiologic pH, they would be expected to complex with cholestyramine in vivo. Although Pastoor *et al.* (1983) investigated cholestyramine in mice and rats and found no enhanced elimination of carbon-14 with a single 1000-mg/kg dose of cholestyramine given at 24 hr after a 10-mg/kg oral dose of ammonium [^{14}C]perfluorooctanoate, the usual application of cholestyramine administered to enhance elimination of xenobiotics is with repeated doses. In the study reported here, we investigated the effect of cholestyramine administered in feed for several days on the rate of fecal elimination of carbon-14 after either a subtoxic intravenous dose of ammonium [^{14}C]perfluorooctanoate ([^{14}C]PFO) or potassium [^{14}C]perfluorooctanesulfonate ([^{14}C]-PFOS).

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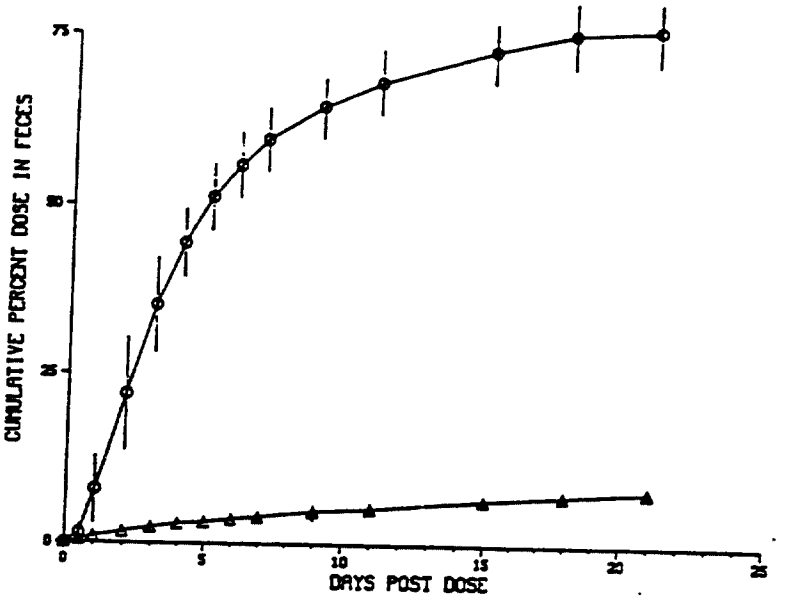

FIG. 1. Cumulative excretion of total carbon-14 in feces after a single intravenous dose of potassium [^{14}C]perfluorooctanesulfonate ([^{14}C]PFOS). Mean dose of [^{14}C]PFOS: cholestyramine treated, 3.4 mg/kg (O); control 3.5 mg/kg (Δ). Total cumulative percentage excreted in feces: cholestyramine treated, 75.8 ± 5.0, control, 8.0 ± 0.8.

sents 4 and 8% of the dose for cholestyramine-treated and control rats, respectively. The mean carbon-14 concentration of plasma and red blood cells with cholestyramine treatment is significantly less than the mean concentration in controls.

DISCUSSION

The carbon-14 present in rat liver after administration of [^{14}C]PFOS or [^{14}C]PFO is probably in the form of anions. (The pK_a of these compounds is <1.0.) Thorough inves-

TABLE 1

EFFECT OF CHOLESTYRAMINE TREATMENT ON CONCENTRATION OF CARBON-14 IN RAT LIVER, PLASMA, AND RED BLOOD CELLS AFTER A SINGLE INTRAVENOUS DOSE OF POTASSIUM [^{14}C]PERFLUOROOCTANESULFONATE[a] ([^{14}C]PFOS) OR AMMONIUM [^{14}C]-PERFLUOROOCTANOATE[b] ([^{14}C]PFO)

Treatment group	Carbon-14 concentration[c]		
	Liver	Plasma	Red blood cells
[^{14}C]PFOS			
Cholestyramine-treated (21 days)	9.4 ± 1.6[d]	0.9 ± 0.1[d]	0.3 ± 0.1[d]
Controls	35.6 ± 5.6	6.9 ± 0.6	1.8 ± 0.4
[^{14}C]PFO			
Cholestyramine-treated (14 days)	12.1 ± 2.1[d]	5.1 ± 1.7[d]	1.8 ± 0.7[d]
Controls	22.3 ± 6.2	14.7 ± 6.8	4.2 ± 2.4

[a] Each rat received 1.13 mg [^{14}C]PFOS; mean dose: cholestyramine-treated rats, 3.4 mg/kg; control rats, 3.5 mg/kg.

[b] Each rat received 4.2 mg [^{14}C]PFO; mean dose: cholestyramine-treated rats, 13.3 mg/kg; control rats .5 mg/kg.

[c] Concentration is expressed as μg eq of radiolabeled compound/g of tissue or ml of fluid.

[d] Significantly different from control values ($p < 0.05$).

remaining in the liver. This difference is most likely due to small additive losses in collection of the many urine and feces samples as well as the small but cumulative error in not correcting for combustion recovery in the many samples (>95%). Since the experimental conditions for cholestyramine-treated and control rats were identical with respect to the dosing, sample collection, and analyses, the less than 100% recovery of carbon-14 (urine, feces, and liver) was judged to not affect the results or conclusion.

Overall, the data support possible utility of cholestyramine in promoting the excretion of perfluorooctanoate and perfluorooctanesulfonate in humans.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the synthesis of ammonium [^{14}C]perfluorooctanoate and potassium [^{14}C]-perfluorooctanesulfonate by F. E. Behr of Commercial Chemicals Division. 3M, and the typing of this manuscript by K. F. Gibson and J. E. Warn of Riker Laboratories.

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