• Gut-Related Radionuclide Studies

Principal Investigator: M. F. Sullivan

Other Investigators: B. M. Miller and J. L. Ryan

Technical Assistance: K. I. Cousineau, K. D. Fisk, and N. M. Goranson

This project is concerned with the behavior of radioactive materials that may be ingested as a consequence of a reactor accident, unavoidable occupational exposure, or after release to the environment and incorporation into the food chain. Current emphasis is directed toward evaluating hazards from ingested actinides as a function of animal age, species, nutrition, and diet, or chemicophysical state of the actinide. It is also concerned with the behavior of actinides that are inhaled and pass through the gastrointestinal (GI) tract after clearance through the lungs.

Recent observations indicate that the influence of chemical form on plutonium absorption observed at high mass levels does not occur at low mass concentrations. For example, at doses of 0.6 μg/kg there was no difference between absorption of the carbonate, citrate or nitrate forms of plutonium. However, at 1.5 mg/kg, the citrate was absorbed in quantities 30 times higher than the nitrate. The opposite effect occurred for neptunium GI absorption. The low-specific-activity isotope, ^{237}Np, gavaged at doses of 22 or 43 mg/kg, was absorbed in quantities from 30 to 50 times greater than the high-specific-activity neptunium isotopes, ^{235}NP and ^{239}Np, at doses that were 1×10^{6} or 2×10^{8}, respectively, less than that of ^{237}Np.

We have also demonstrated that materials such as citrus fruit juices and calcium, as well as drugs that affect GI function (such as aspirin and DTPA), markedly influence GI absorption of plutonium. Such studies provide evidence that diet and nutritional state should be considered in establishing safe limits for radionuclides that may be ingested.

Effects of Chemical Form and Plutonium Concentration on Gastrointestinal Absorption by Adult or Neonatal Rodents

From previous studies, it was concluded that 10 times more plutonium is absorbed from the GI tract when administered as the citrate than when administered in less soluble forms, such as the nitrate or carbonate. To determine the importance of compound form at very low plutonium concentrations, we compared the absorption of ^{239}Pu from relatively concentrated solutions in 5% citrate or 0.01 M nitric acid, with absorption of mixed $^{237}/^{239}$Pu at very low concentrations in similar citrate or nitrate solutions.

Groups of adult, male Swiss-Webster mice received 0.25 ml of either the ^{239}Pu or $^{237}/^{239}$Pu preparations intragastrically through polyethylene tubing. Litters of 2-day-old rats were divided approximately equally and received 0.1 ml of solutions of either high or low concentrations of plutonium citrate, carbonate or nitrate. All animals were killed at 7 days after gavage. Those given ^{239}Pu were measured for their alpha radioactivity. Those given $^{237}/^{239}$Pu were counted for the photon emissions of ^{237}Pu, both in a whole-body counter and in a deep-well gamma counter.

Results obtained after gavage of adult mice are summarized in Table 1. The marked difference in absorption of ^{239}Pu citrate and nitrate, fed at high mass levels, was not observed when much lower mass levels of $^{237}/^{239}$Pu were fed; nor was there a significant difference between absorption of the citrate and the less-soluble Pu carbonate.

Our previous comparison (Annual Report, 1980) of the absorption of ^{237}Pu and ^{239}Pu nitrate demonstrated that absorption was inversely related to the mass of Pu administered. The data in Table 1 support that observation.

We also found that mass influenced absorption in neonatal rats (Table 2), although to a lesser extent than in adult animals. Chemical form also affected absorption in neonatal rats at high Pu doses; retention after gavage of ^{239}Pu citrate was about three times that after ^{239}Pu nitrate. At lower mass levels, no such effect was observed.

TABLE 1. The Effect of Concentration and/or Chemical Form on Gastrointestinal Absorption of Plutonium by Mice.

Pu Isotope	^{239}Pu		$^{237/239}Pu$		
Pu Compound	Citrate	Nitrate	Citrate	Nitrate	Carbonate
Activity Administered, μCi/kg	91	91	1	1	1
Mass Administered, μg/kg	1480	1480	0.6	0.6	0.6
No. of Animals	10	10	19	19	5
Time of Necropsy, days	7	7	7	7	7
Tissue	Percent of Gavaged Pu Dose ± SEM				
Carcass, (minus skin and GI tract)	0.2	0.005	0.08	0.07	0.14
Liver	0.08	0.001	0.05	0.01	0.03
Total	0.28 ± 0.03	0.006 ± 0.001	0.13 ± 0.02	0.08 ± 0.02	0.17 ± 0.07

TABLE 2. The Effect of Concentration and/or Chemical Form on Gastrointestinal Absorption of Plutonium by Neonatal Rats.

Pu Isotope	^{239}Pu		$^{237/239}Pu$	
Pu Compound	Citrate	Nitrate	Citrate	Nitrate
Activity Administered, μCi/kg	115	115	0.9	0.9
Mass Administered, μg/kg	1875	1875	0.6	0.6
No. of Animals	7	10	11	6
Time of Necropsy, days	7	7	7	7
Tissue	Percent of Gavaged Dose ± SEM			
Carcass (minus skin and and GI tract)	2.5	0.8	1.6	2.1
Liver	0.3	0.2	0.2	0.3
Total	2.8 ± 0.8	1.0 ± 0.1	1.8 ± 0.1	2.4 ± 0.3
GI Tract and Content	27 ± 6	36 ± 3	62 ± 2	67 ± 1

Effect of Mass on Gastrointestinal Absorption of Neptunium

Neptunium may be the most hazardous nuclear waste product in the distant future (>2000 yr) because of its long half-life isotope ^{237}Np (2.1 x 10^6 yr) and its reactivity in biological systems. Our previous results (Annual Reports, 1973, 1975) indicated that the absorption of ^{237}Np nitrate was about 10 times higher (in adult rats) than that of any other transuranic studied. Earlier data had suggested that absorption was directly related to mass; however we had found the opposite to be true for plutonium (Annual Report, 1980). We therefore conducted experiments to study the GI absorption for ^{237}Np ($T_{\frac{1}{2}}$, 2.1 x 10^6 yr), ^{235}Np ($T_{\frac{1}{2}}$, 396 days), and ^{239}Np ($T_{\frac{1}{2}}$, 2.3 days). Results are summarized in Table 3. There was very little difference in the absorption of ^{235}Np and ^{239}Np, although the mass administered differed by a factor of 180. On the other hand, absorption of either ^{235}Np or ^{239}Np was about 50 times lower than that of ^{237}Np, the mass of ^{237}Np administered being 10^6 to 10^8 times that of ^{235}Np or ^{239}Np. Doubling the mass of ^{237}Np administered almost doubled the amount absorbed, suggesting that chemically toxic effects of the large quantity of neptunium administered may have caused the increased absorption.

Because the quantity of ^{235}Np was limited, only a few rats could be studied; mice were employed to extend the data to more animals and to another species. The ^{235}Np retention in mice could be measured by whole-body counting of the X-ray emissions. A comparison of the mouse and rat data (Table 3) indicates no species difference in absorption.

An experiment with ^{239}Np was performed with neonatal rats for comparison with previous ^{237}Np neonatal rat studies (Annual Reports, 1974, 1975). Those earlier studies showed GI absorption of ^{237}Np in 2- and 9-day-old rats of 0.8 and 1.2%, respectively. The ^{239}Np data in Table 4 show a similar absorption in 2- and 9-day-old rats. Both age groups absorbed at least 25 times the adult value. The percentage retained in the gut was, however, about five times higher for ^{239}Np than the earlier value observed for ^{237}Np. Unlike the case for ^{237}Np, the comparative behavior of ^{239}Np in neonatal and adult rats is quite similar to that of plutonium.

TABLE 3. The Effect of Mass Administered on Gastrointestinal Absorption of Neptunium Nitrate by Adult Rats and Mice.

Np Isotope	^{237}Np		^{235}Np		^{239}Np
Activity Administered, μCi/kg	30	15	18	90	42
Mass Administered, μg/kg	43,000	21,700	0.04	0.13	0.00022
Species	Rats	Rats	Rats	Mice	Rats
No. of Animals	6	6	4	8	10
Time of Necropsy, days	7	7	7	7	3
Tissue	Percent of Gavaged Dose ± SEM				
Carcass (minus skin)	1.5	0.9	0.02	0.03	0.03
Liver	0.24	0.09	0.007	0.01	0.006
Urine	1.0	0.5	0.03	--	0.01
Total	2.74 ± 0.4	1.5 ± 0.2	0.06 ± 0.01	0.06 ± 0.01	0.04 ± 0.01

TABLE 4. The Effect of Age on Gastrointestinal Absorption of ^{239}Np Nitrate by Rats.

Age at Gavage	Adult	9 Day	2 Day
Activity Administered, μCi/kg	50	100	185
Mass Administered, μg/kg	2.2×10^{-4}	4.3×10^{-4}	8×10^{-4}
No. of Rats	10	11	9
Time of Necropsy, days	3	4	4
Tissue	Percent of Gavaged Dose ± SEM		
Carcass (minus skin and GI tract)	0.027	0.87	1.24
Liver	0.006	0.03	0.03
Total	0.03 ± 0.006	0.90 ± 0.05	1.27 ± 0.10
GI Tract (content)	--	59.6 ± 1.3	72.6 ± 8.0

The Effect of Diet, Aspirin and DTPA on the Absorption of ^{238}Pu from the GI Tract of Rats

We previously demonstrated (Annual Reports, 1971, 1980) that the effects of fasting, citric acid, milk and DTPA on the GI absorption of plutonium all resulted in increased absorption. Orally administered DTPA caused enhanced absorption, demonstrated by increased urinary excretion of Pu. Since citric acid enhanced plutonium absorption, it was expected that orange juice might also cause an increase in transport, as it does for lead. Aspirin (acetylsalicylic acid) may also affect transport because of its damaging effects on the mucosa. Calcium deficiency and intravenously administered EDTA causes increased lead toxicity by increasing GI absorption.

To test the effect of orange juice, 2 ml were administered intragastrically to rats that were either fasted for 24 hr before gavage or fed ad libitum. The orange juice gavage was followed immediately by 1 ml of 0.01 M HNO_3 containing ^{238}Pu. The results (Table 5) indicate no increase in absorption due to fasting but a 7-fold increase due to the presence of orange juice in the GI tract.

To test the effect of aspirin, a suspension in 2% methyl cellulose was administered daily by gavage at doses of either 200 or 400 mg/kg. On the third day of treatment, 1.0 ml of 0.01 M HNO_3 containing ^{238}Pu was also gavaged. The results (Table 6) show no increase in liver retention or urinary excretion; however, the amount in bone doubled, causing a 2-fold higher retention in treated animals than in controls. The effect of aspirin was not dose-dependent.

TABLE 5. The Effect of Orange Juice on Gastrointestinal Absorption of ^{238}Pu Nitrate (1.44 μg/kg) by Fed and Fasted Rats.[a]

	Percent of Gavaged Dose ± SEM			
	^{238}Pu Control		^{238}Pu + Orange Juice	
Tissue	Non-Fasted	Fasted	Non-Fasted	Fasted
Carcass	0.02	0.02	0.1	0.11
Liver	0.001	0.002	0.02	0.03
Urine	0.003	0.006	0.017	0.005
Total Absorbed	0.02 ± 0.01	0.03 ± 0.01	0.14 ± 0.05	0.15 ± 0.02

[a]4 rats per group, see text for details.

TABLE 6. the Effect of Aspirin on Gastrointestinal Absorption of ^{238}Pu Nitrate (40 μCi/kg) by Rats.[a]

	Percent of Gavaged Dose ± SEM		
Tissue	Control	0.05 mg Aspirin/kg	0.1 mg Aspirin/kg
Carcass	0.017	0.049	0.045
Liver	0.005	0.006	0.006
Urine	0.006	0.007	0.007
Total Absorbed	0.029 ± 0.007	0.062 ± 0.01	0.058 ± 0.02

[a]6 rats per group, see text for details.

To produce a calcium deficiency, a special (calcium-deficient) diet supplied by US Biochemical Corp. (Cleveland, OH) was fed to adult or weanling rats for 2 wk. They were then gavaged with 1 ml of 0.01 M HNO_3 containing ^{238}Pu and maintained on the calcium-deficient diet until sacrifice, 7 days later. The results (Table 7) indicate that absorption and retention of ^{238}Pu was substantially increased. The adult values increased 20-fold, whereas the weanling values increased about seven times.

When DTPA was injected intravenously (0.5 mM/kg) immediately before gavage with 1 ml of 0.01 M HNO_3 containing ^{238}Pu, an increase in urinary excretion (Table 8) was the major indication of an increase in absorption. It was increased about 50 times over that of control rats. Retention in every tissue measured was also reduced by DTPA.

These results demonstrate that plutonium GI absorption may be increased by diet changes or drug treatment. Those effects may be produced directly, by the presence of the nutrient or drug within the GI tract at the same time as the actinide, or they may result from an indirect, systemic effect.

TABLE 7. The Effect of Calcium Deficiency on Gastrointestinal Absorption of ^{238}Pu Nitrate by Adult and Weanling Rats.[a]

	Percent of Gavaged Dose ± SEM			
	Adult		Weanling	
Tissue	Control	Ca Deficient	Control	Ca Deficient
Carcass (minus skin and GI tract)	0.01	0.26	0.06	0.34
Liver	0.002	0.02	0.004	0.04
Urine	0.0008	0.01	0.004	0.12
Total Absorbed	0.013 ± 0.004	0.29 ± 0.04	0.07 ± 0.02	0.53 ± 0.13

[a]10-12 rats per group, see text for details.

TABLE 8. The Effect of Intravenously Administered DTPA (0.5 mM/kg) on Gastrointestinal Absorption of ^{238}Pu Nitrate by Rats.[a]

	Percent of Gavaged Dose ± SEM	
Tissue	^{238}Pu Control	^{238}Pu + DTPA
Carcass (minus skin and GI tract)	0.017	0.016
Liver	0.005	0.0004
Urine	0.006	1.3
Total Absorbed	0.029 ± 0.007	1.3 ± 0.4

[a]6 rats per group, see text for details.